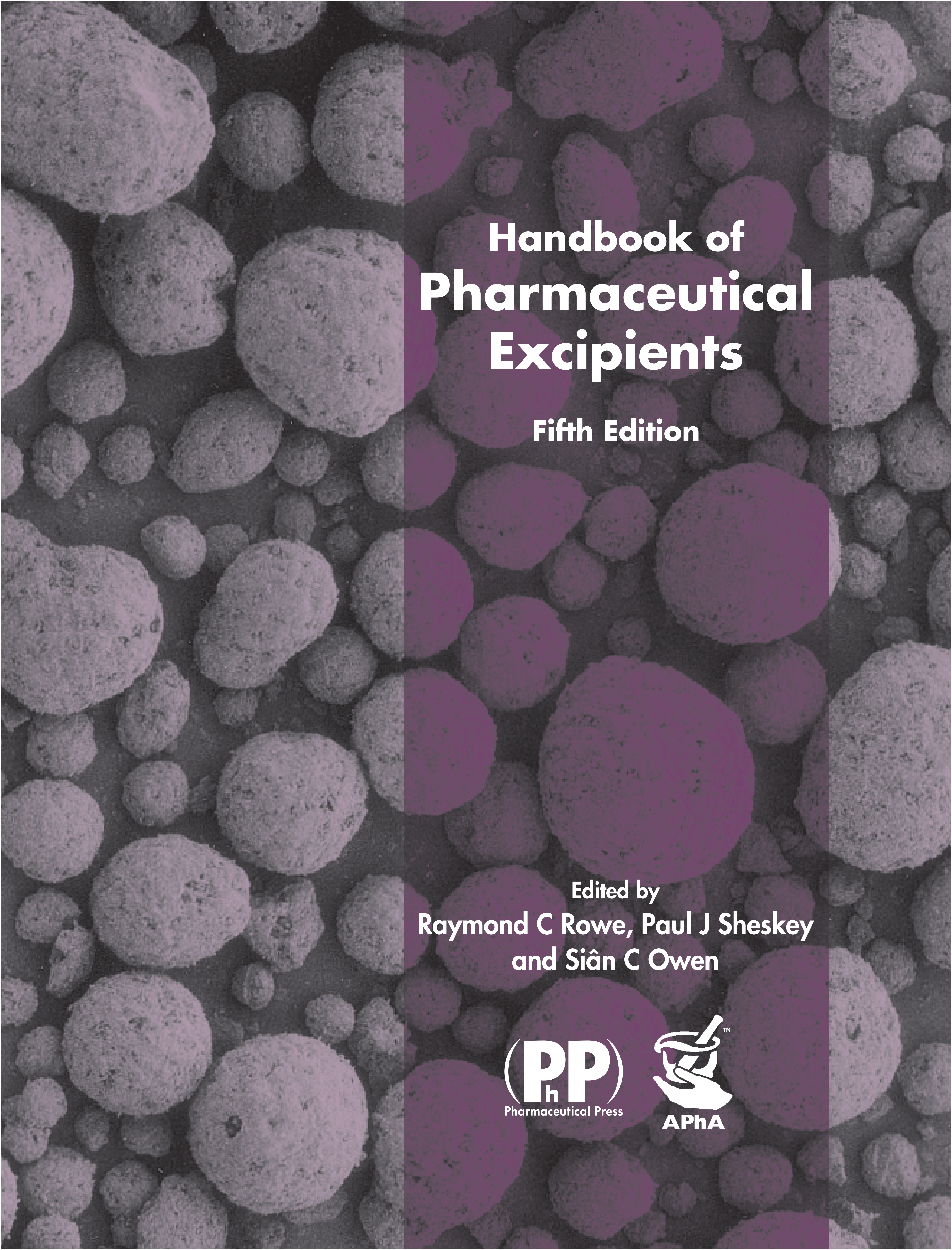
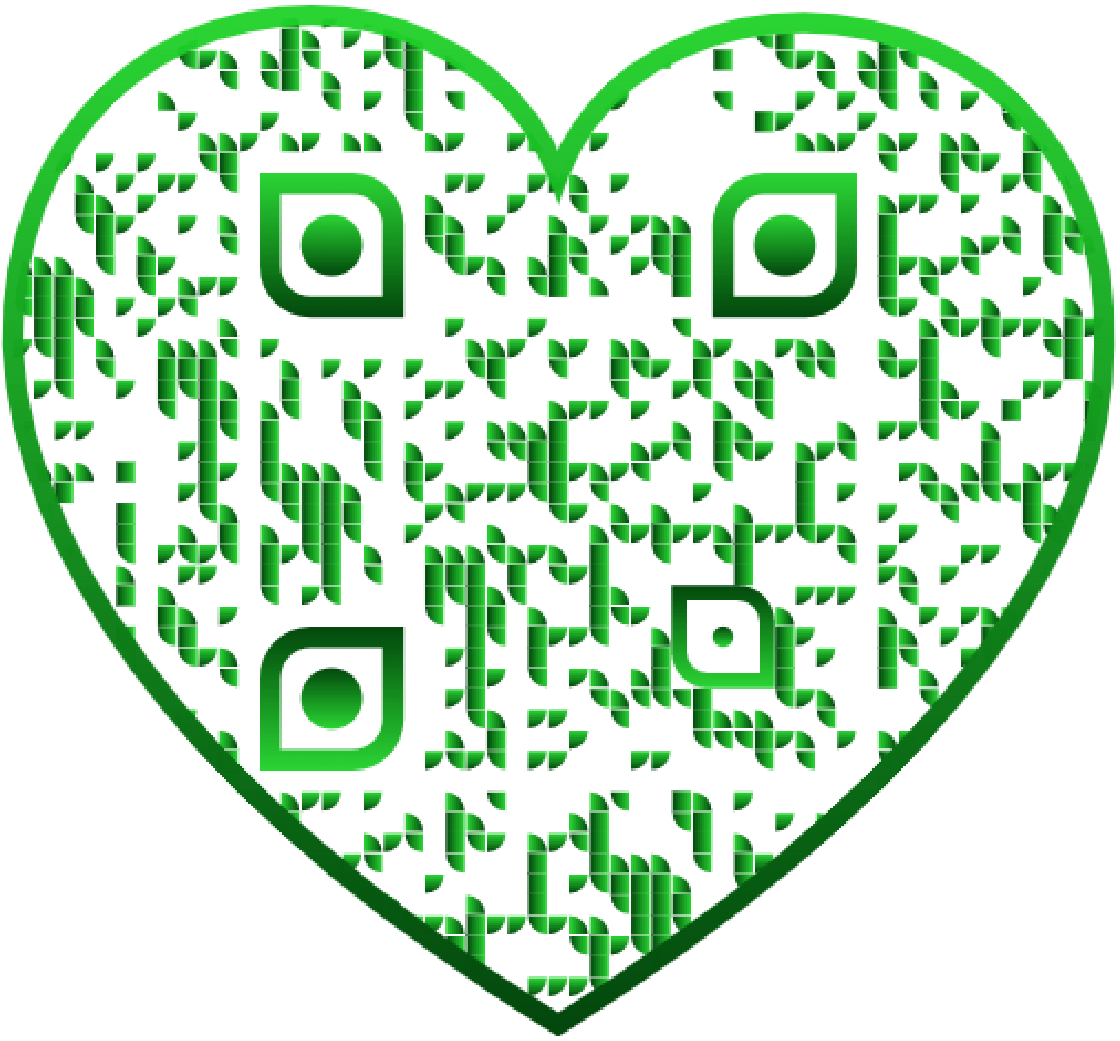


Handbook of Pharmaceutical Excipients

Fifth Edition

Edited by
Raymond C Rowe, Paul J Sheskey
and Siân C Owen

Pharmaceutical Press
APhA



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FIFTH EDITION

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New Monographs

The following new monographs have been added to the *Handbook of Pharmaceutical Excipients, 5th edition*.

Acetone
Agar
Aluminum Hydroxide Adjuvant
Aluminum Oxide
Aluminum Phosphate Adjuvant
Ammonium Alginate
Aluminum Stearate
Boric Acid
Calcium Alginate
Cetylpyridinium Chloride
Copovidone
Dimethylacetamide
Disodium Edetate
Erythorbic Acid
Erythritol
Ethyl Lactate
Ethylene Vinyl Acetate
Hectorite
Hydroxypropyl Starch
Hypromellose Acetate Succinate
Inulin
Iron Oxides
Isomalt
Lactose, Anhydrous
Lactose, Monohydrate
Lactose, Spray-Dried
Lauric Acid
Leucine
Linoleic Acid
Macrogol 15 Hydroxystearate
Myristic Acid
Neohesperidin Dihydrochalcone
Octyldodecanol
Oleyl Alcohol
Palmitic Acid
Pectin
Polycarbophil
Poly(methylvinyl ether/maleic anhydride)
Potassium Alginate
2-Pyrrolidone
Raffinose
Saponite
Sodium Acetate
Sodium Borate
Sodium Hyaluronate
Sodium Lactate
Sodium Sulfite
Sulfobutylether β-Cyclodextrin
Thaumatin
Thymol
Zinc Acetate

Related Substances

Acetic acid
Activated attapulgite
Aleuritic acid
d-Alpha tocopherol
d-Alpha tocopheryl acetate
dl-Alpha tocopheryl acetate
d-Alpha tocopheryl acid succinate
dl-Alpha tocopheryl acid succinate
Aluminum distearate
Aluminum monostearate
Amylopectin
α-Amylose
Anhydrous citric acid
Anhydrous sodium citrate
Anhydrous sodium propionate
Artificial vinegar
Bacteriostatic water for injection
Bentonite magma
Beta tocopherol
Beta-carotene
n-Butyl lactate
Butylparaben sodium
Calcium ascorbate
Calcium cyclamate
Calcium polycarbophil
Calcium propionate
Calcium silicate
Calcium sorbate
Calcium sulfate hemihydrate
Capric acid
Carbon dioxide-free water
Cationic emulsifying wax
Ceratonia extract
Cetylpyridinium bromide
Chlorhexidine acetate
Chlorhexidine gluconate
Chlorhexidine hydrochloride
Chlorodifluoromethane
Chlorophenoxyethanol
Corn syrup solids
m-Cresol
o-Cresol
p-Cresol
Crude olive-pomace oil
Cyclamic acid
De-aerated water
Dehydrated alcohol
Delta tocopherol
Denatured alcohol
Dextrose anhydrous
Diazolidinyl urea
Dibasic potassium phosphate
Diethylene glycol monopalmitostearate
Dilute acetic acid
Dilute alcohol
Dilute ammonia solution
Dilute hydrochloric acid
Dilute phosphoric acid
Dilute sulfuric acid
Dimethyl-β-cyclodextrin
Dioctyl phthalate
Dipotassium edetate
Docusate calcium
Docusate potassium
Dodecyl gallate
Dodecyltrimethylammonium bromide
Edetate calcium disodium
Eglumine
Ethyl gallate
Ethylene glycol monopalmitate
Ethylene glycol monostearate
Ethyl linoleate
Ethylparaben potassium
Ethylparaben sodium
Extra virgin olive oil
Fine virgin olive oil
Fuming sulfuric acid
Gamma tocopherol
Hard water
Hesperidin
Hexadecyltrimethylammonium bromide
High-fructose syrup
Hyaluronic acid
Hydrogenated lanolin
Hydrogenated vegetable oil, type II
2-Hydroxyethyl-β-cyclodextrin
2-Hydroxypropyl-β-cyclodextrin
3-Hydroxypropyl-β-cyclodextrin
Indigo carmine
Invert sugar
Isotrehalose
Lampante virgin olive oil
Lanolin alcohols ointment
DL-Leucine
Liquefied phenol
Liquid fructose
Magnesium carbonate anhydrous
Magnesium carbonate hydroxide
Magnesium lauryl sulfate
Magnesium metasilicate
Magnesium orthosilicate
Magnesium trisilicate anhydrous
D-Malic acid
L-Malic acid
d-Menthol
l-Menthol
Methyl lactate
Methyl linoleate
Methyl methacrylate
Methyl oleate

Methylparaben potassium
Methylparaben sodium
N-Methylpyrrolidone
Microcrystalline cellulose and carboxymethylcellulose sodium
Microcrystalline cellulose and carrageenan
Microcrystalline cellulose and guar gum
Modified lanolin
Monobasic potassium phosphate
Montmorillonite
Myristyl alcohol
Neotrehalose
Normal magnesium carbonate
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Oleyl oleate
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Palmitin
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Phenoxypropanol
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Poly(methyl methacrylate)
Potassium bisulfite
Potassium myristate
Potassium propionate
Powdered fructose
Propan-1-ol
(*S*)-Propylene carbonate
Propylparaben potassium
Propylparaben sodium
Purified bentonite
Purified stearic acid
Quaternium 18-hectorite
Rapeseed oil
Refined almond oil
Refined olive-pomace oil
Saccharin ammonium
Saccharin calcium
Self-emulsifying glyceryl monostearate
Shellolic acid
Sodium bisulfite
Sodium borate anhydrous
Sodium edetate
Sodium erythorbate
Sodium laurate
Sodium myristate
Sodium palmitate
Sodium sorbate
Sodium sulfite heptahydrate
Soft water
Sorbitol solution 70%
Spermaceti wax
Stearalkonium hectorite
Sterile water for inhalation
Sterile water for injection
Sterile water for irrigation
Sunset yellow FCF
Synthetic paraffin
DL-(±)-Tartaric acid
Tartrazine
Theobroma oil
Tocopherols excipient
Tribasic sodium phosphate
Trimethyl-β-cyclodextrin
Trimethyltetradecylammonium bromide
Trisodium edetate
Virgin olive oil
Water for injection
White petrolatum
Zinc propionate

Preface

Pharmaceutical dosage forms contain both pharmacologically active compounds and excipients added to aid the formulation and manufacture of the subsequent dosage form for administration to patients. Indeed, the properties of the final dosage form (i.e. its bioavailability and stability) are, for the most part, highly dependent on the excipients chosen, their concentration and interaction with both the active compound and each other. No longer can excipients be regarded simply as inert or inactive ingredients, and a detailed knowledge not only of the physical and chemical properties but also of the safety, handling and regulatory status of these materials is essential for formulators throughout the world. In addition, the growth of novel forms of delivery has resulted in an increase in the number of the excipients being used and suppliers of excipients have developed novel excipient mixtures and new physical forms to improve their properties. The *Handbook of Pharmaceutical Excipients* has been conceived as a systematic, comprehensive resource of information on all of these topics

The first edition of the *Handbook* was published in 1986 and contained 145 monographs. This was followed by the second edition in 1994 containing 203 monographs, the third edition in 2000 containing 210 monographs and the fourth edition in 2003 containing 249 monographs. Since 2000, the data has also been available on CD-ROM, updated annually, and from 2004 online. This new printed edition with its companion CD-ROM, *Pharmaceutical Excipients 5*, contains 300 monographs compiled by over 120 experts in pharmaceutical formulation or excipient manufacture from Australia, Europe, India and the USA. All the monographs have been reviewed and revised in the light of current knowledge. There has been a greater emphasis on including published data from primary sources although some data from laboratory projects included in previous editions have been retained where relevant. Variations in test methodology can have significant effects on the data generated (especially in the case of the compactability of an excipient), and thus cause confusion. As a consequence, the editors have been more selective in including data relating to the physical properties of an excipient. However, comparative data that show differences between either source or batch of a specific excipient have been retained as this was considered relevant to the behavior of a material in practice. The Suppliers Directory (Appendix I) has also been completely updated with many more international suppliers included.

In a systematic and uniform manner, the *Handbook of Pharmaceutical Excipients* collects essential data on the physical properties of excipients such as: boiling point, bulk and tap density, compression characteristics, hygroscopicity, flowability, melting point, moisture content, moisture-absorption isotherms, particle size distribution, rheology, specific surface area, and solubility. Scanning electron microphotographs (SEMs) are also included for many of the excipients. The *Handbook* contains information from various international sources and personal observation and comments from monograph authors, steering committee members, and the editors.

All of the monographs in the *Handbook* are thoroughly cross-referenced and indexed so that excipients may be identified by either a chemical, a nonproprietary, or a trade name. Most monographs list related substances to help the formulator to develop a list of possible materials for use in a new dosage form or product. Related substances are not directly substitutable for each other but, in general, they are excipients that have been used for similar purposes in various dosage forms.

The *Handbook of Pharmaceutical Excipients* is a comprehensive, uniform guide to the uses, properties, and safety of pharmaceutical excipients, and is an essential reference source for those involved in the development, production, control, or regulation of pharmaceutical preparations. Since many pharmaceutical excipients are also used in other applications, the *Handbook of Pharmaceutical Excipients* will also be of value to persons with an interest in the formulation or production of confectionery, cosmetics, and food products.

Arrangement

The information consists of monographs that are divided into 22 sections to enable the reader to find the information of interest easily. Although it was originally intended that each monograph contain only information about a single excipient, it rapidly became clear that some substances or groups of substances should be discussed together. This gave rise to such monographs as 'Coloring Agents' and 'Hydrocarbons'. In addition, some materials have more than one monograph depending on the physical characteristics of the material, e.g. Starch versus Pregelatinized Starch. Regardless of the complexity of the monograph they are all divided into 22 sections as follows:

1. Nonproprietary Names
2. Synonyms
3. Chemical Name and CAS Registry Number
4. Empirical Formula and Molecular Weight
5. Structural Formula
6. Functional Category
7. Applications in Pharmaceutical Formulation or Technology
8. Description
9. Pharmacopeial Specifications
10. Typical Properties
11. Stability and Storage Conditions
12. Incompatibilities
13. Method of Manufacture
14. Safety
15. Handling Precautions
16. Regulatory Status
17. Related Substances
18. Comments
19. Specific References
20. General References
21. Authors
22. Date of Revision

Descriptions of the sections appear below with information from an example monograph if needed.

Section 1, Nonproprietary Names, lists the excipient names used in the current British Pharmacopoeia, European Pharmacopeia, Japanese Pharmacopeia, and the United States Pharmacopeia/National Formulary.

Section 2, Synonyms, lists other names for the excipient, including trade names used by suppliers (shown in italics). The inclusion of one supplier's trade name and the absence of others should in no way be interpreted as an endorsement of one supplier's product over the other. The large number of suppliers internationally makes it impossible to include all the trade names.

Section 3, Chemical Name and CAS Registry Number, indicates the unique Chemical Abstract Services number for an excipient along with the chemical name, e.g., Acacia [9000-01-5].

Sections 4 and 5, Empirical Formula and Molecular Weight and Structural Formula, are self-explanatory. Many excipients are not pure chemical substances, in which case their composition is described either here or in Section 8.

Section 6, Functional Category, lists the function(s) that an excipient is generally thought to perform, e.g., diluent, emulsifying agent, etc.

Section 7, Applications in Pharmaceutical Formulation or Technology, describes the various applications of the excipient.

Section 8, Description, includes details of the physical appearance of the excipient, e.g., white or yellow flakes, etc.

Section 9, Pharmacopeial Specifications, briefly presents the compendial standards for the excipient. Information included is obtained from the British Pharmacopoeia (BP), European Pharmacopeia (PhEur), Japanese Pharmacopeia (JP), and the United States Pharmacopeia/National Formulary (USP/USPNF). Information from the JP, USP and USPNF are included if the substance is in those compendia. Information from the PhEur is also included. If the excipient is not in the PhEur but is included in the BP, information is included from the BP. Pharmacopeias are continually updated with most now being produced as annual editions. However, although efforts were made to include up-to-date information at the time of publication of this edition, the reader is advised to consult the most current pharmacopeias or supplements.

Section 10, Typical Properties, describes the physical properties of the excipient which are not shown in Section 9. All data are for measurements made at 20°C unless otherwise indicated. Where the solubility of the excipient is described in words, the following terms describe the solubility ranges:

Very soluble	1 part in less than 1
Freely soluble	1 part in 1–10
Soluble	1 part in 10–30
Sparingly soluble	1 part in 30–100
Slightly soluble	1 part in 100–1000
Very slightly soluble	1 part in 1000–10 000
Practically insoluble or insoluble	1 part in more than 10 000

Where practical, data typical of the excipient or comparative data representative of different grades or sources of a material are included, the data being obtained from either the primary or the manufacturers' literature. In previous editions of the *Handbook* a laboratory project was undertaken to determine data for a variety of excipients and in some instances this data has been retained. For a description of the specific methods used to generate the data readers should consult the appropriate previous edition(s) of the *Handbook*.

Section 11, Stability and Storage Conditions, describes the conditions under which the bulk material as received from the supplier should be stored. In addition some monographs report on storage and stability of the dosage forms that contain the excipient.

Section 12, Incompatibilities, describes the reported incompatibilities for the excipient either with other excipients or with active ingredients. If an incompatibility is not listed it does not mean it does not occur but simply that it has not been reported or is not well known. Every formulation should be tested for incompatibilities prior to use in a commercial product.

Section 13, Method of Manufacture, describes the common methods of manufacture and additional processes that are used to give the excipient its physical characteristics. In some cases the possibility of impurities will be indicated in the method of manufacture.

Section 14, Safety, describes briefly the types of formulations in which the excipient has been used and presents relevant data concerning possible hazards and adverse reactions that have been reported. Relevant animal toxicity data are also shown.

Section 15, Handling Precautions, indicates possible hazards associated with handling the excipient and makes recommendations for suitable containment and protection methods. A familiarity with current good laboratory practice (GLP) and current good manufacturing practice (GMP) and standard chemical handling procedures is assumed.

Section 16, Regulatory Status, describes the accepted uses in foods and licensed pharmaceuticals where known. However, the status of excipients varies from one nation to another, and appropriate regulatory bodies should be consulted for guidance.

Section 17, Related Substances, lists excipients similar to the excipient discussed in the monograph.

Section 18, Comments, includes additional information and observations relevant to the excipient. Where appropriate, the different grades of the excipient available are discussed. Comments are the opinion of the listed author(s) unless referenced or indicated otherwise.

Section 19, Specific References, is a list of references cited within the monograph.

Section 20, General References, lists references which have general information about this type of excipient or the types of dosage forms made with these excipients.

Section 21, Authors, lists the current authors of the monograph in alphabetical order. Authors of previous versions of the monograph are shown in previous printed editions of the text.

Section 22, Date of Revision, indicates the date on which changes were last made to the text of the monograph.

Acknowledgments

A publication containing so much detail could not be produced without the help of a large number of pharmaceutical scientists based world-wide. The voluntary support of over 120 authors has been acknowledged as in previous editions, but the current editors would like to thank them all personally for their contribution. Grateful thanks also go to the members of the International Steering Committee who advised the editors and publishers on all aspects of the *Handbook* project. Steering Committee members also diligently reviewed all of the monographs before their publication. Many authors and Steering Committee members have been involved in previous editions of the *Handbook*. For others, this was their first edition although not, we hope, their last. Walter Chambliss and John Hogan retired from the International Steering Committee during the preparation of this edition and we extend our thanks for their support over many years. Thanks are also extended to excipient manufacturers and suppliers who provided helpful information on their products.

Thanks are also gratefully extended to the staff of the Pharmaceutical Press and American Pharmacists Association who were involved in the production of the *Handbook*: Eric Connor, Tamsin Cousins, Simon Dunton, Laurent Galichet, Julian Graubart, Louise McIndoe, Karl Parsons, Paul Weller, and John Wilson. Once again, the diligent copy-editing and challenging questions asked by Len Cegielka helped the authors and editors, we hope, to express their thoughts clearly, concisely, and accurately.

Raymond C Rowe, Paul J Sheskey and Siân C Owen
August 2005

Notice to Readers

The *Handbook of Pharmaceutical Excipients* is a reference work containing a compilation of information on the uses and properties of pharmaceutical excipients, and the reader is assumed to possess the necessary knowledge to interpret the information that the *Handbook* contains. The *Handbook of Pharmaceutical Excipients* has no official status and there is no intent, implied or otherwise, that any of the information presented should constitute standards for the substances. The inclusion of an excipient, or a description of its use in a particular application, is not intended as an endorsement of that excipient or application. Similarly, reports of incompatibilities or adverse reactions to an excipient, in a particular application, may not necessarily prevent its use in other applications. Formulators should perform suitable experimental studies to satisfy themselves and regulatory bodies that a formulation is efficacious and safe to use.

While considerable efforts were made to ensure the accuracy of the information presented in the *Handbook*, neither the publishers nor the compilers can accept liability for any errors or omissions. In particular, the inclusion of a supplier within the Suppliers Directory is not intended as an endorsement of that supplier or its products and, similarly, the unintentional omission of a supplier or product from the directory is not intended to reflect adversely on that supplier or its product.

Although diligent effort was made to use as recent compendial information as possible, compendia are frequently revised and the reader is urged to consult current compendia, or supplements, for up-to-date information, particularly as efforts are currently in progress to harmonize standards for excipients.

Data presented for a particular excipient may not be representative of other batches or samples.

Relevant data and constructive criticism are welcome and may be used to assist in the preparation of any future editions or electronic versions of the *Handbook*. The reader is asked to send any comments to the Editor, Handbook of Pharmaceutical Excipients, Royal Pharmaceutical Society of Great Britain, 1 Lambeth High Street, London SE1 7JN, UK, or Editor, Handbook of Pharmaceutical Excipients, American Pharmacists Association, 2215 Constitution Avenue, NW, Washington, DC 20037-2985, USA.

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Abbreviations

Some units, terms, and symbols are not included in this list as they are defined in the text. Common abbreviations have been omitted. The titles of journals are abbreviated according to the general style of the *Index Medicus*.

≈	approximately.
Ad	Addendum.
ADI	acceptable daily intake.
approx	approximately.
atm	atmosphere.
BAN	British Approved Name.
bp	boiling point.
BP	British Pharmacopoeia.
BS	British Standard (specification).
BSI	British Standards Institution.
cal	calorie(s).
CAS	Chemical Abstract Service.
CFC	chlorofluorocarbon.
cm	centimeter(s).
cm^2	square centimeter(s).
cm^3	cubic centimeter(s).
cmc	critical micelle concentration.
CNS	central nervous system.
cP	centipoise(s).
cSt	centistoke(s).
CTFA	Cosmetic, Toiletry, and Fragrance Association.
D&C	designation applied in USA to dyes permitted for use in drugs and cosmetics.
DoH	Department of Health (UK).

DSC	differential scanning calorimetry.
EC	European Community.
e.g.	*exemplit gratia*, 'for example'.
EINECS	European Inventory of Existing Commercial Chemical Substances.
et al	*et alii*, 'and others'.
EU	European Union.
FAO	Food and Agriculture Organization of the United Nations.
FAO/ WHO	Food and Agriculture Organization of the United Nations *and the* World Health Organization.
FCC	Food Chemicals Codex.
FDA	Food and Drug Administration of the USA.
FD&C	designation applied in USA to dyes permitted for use in foods, drugs, and cosmetics.
FFBE	Flat face beveled edge.
g	gram(s).
GMP	Good Manufacturing Practice.
GRAS	generally recognized as safe by the Food and Drug Administration of the USA.
HC	hydrocarbon.
HCFC	hydrochlorofluorocarbon.
HFC	hydrofluorocarbon.
HIV	human immunodeficiency virus.
HLB	hydrophilic–lipophilic balance.
HSE	Health and Safety Executive (UK).
i.e.	*id est*, 'that is'.
IM	intramuscular.
INN	International Nonproprietary Name.
IP	intraperitoneal.
ISO	International Organization for Standardization.
IU	International Units.
IV	intravenous.
J	joule(s).
JP	Japanese Pharmacopeia.
JPE	Japanese Pharmaceutical Excipients
kcal	kilocalorie(s).
kg	kilogram(s).
kJ	kilojoule(s).
kPa	kilopascal(s).
L	liter(s).
LAL	*Limulus* amoebocyte lysate.
LC$_{50}$	a concentration in air lethal to 50% of the specified animals on inhalation.
LD$_{50}$	a dose lethal to 50% of the specified animals or microorganisms.
Ld$_{Lo}$	lowest lethal dose for the specified animals or microorganisms.
m	meter(s).
m^2	square meter(s).
m^3	cubic meter(s).
M	molar.
max	maximum.
MCA	Medicines Control Agency (UK).
mg	milligram(s).
MIC	minimum inhibitory concentration.
min	minute(s) *or* minimum.
mL	milliliter(s).
mm	millimeter(s).
mM	millimolar.
mm^2	square millimeter(s).
mm^3	cubic millimeter(s).
mmHg	millimeter(s) of mercury.
mmol	millimole(s).
mN	millinewton(s).
mol	mole(s).
mp	melting point.
mPa	millipascal(s).
MPa	megapascal(s).
μg	microgram(s).
μm	micrometer(s).
N	newton(s) *or* normal (concentration).
nm	nanometer(s).
o/w	oil-in-water.
o/w/o	oil-in-water-in-oil.
Pa	pascal(s).
pH	the negative logarithm of the hydrogen ion concentration.
PhEur	European Pharmacopeia.
pK$_a$	the negative logarithm of the dissociation constant.
pph	parts per hundred.
ppm	parts per million.
psia	pounds per square inch absolute.
RDA	recommended dietary allowance (USA).
rpm	revolutions per minute.
s	second(s).
SC	subcutaneous.
SEM	scanning electron microscopy *or* scanning electron microphotograph.
SI	Statutory Instrument *or* SystÜme International d'Unites (International System of Units).
TPN	total parental nutrition.
TWA	time weighted average.
UK	United Kingdom.
US *or* USA	United States of America.
USAN	United States Adopted Name.
USP	The United States Pharmacopeia.
USPNF	The United States Pharmacopeia National Formulary.
UV	ultraviolet.
v/v	volume in volume.
v/w	volume in weight.
WHO	World Health Organization.
w/o	water-in-oil.
w/o/w	water-in-oil-in-water.
w/v	weight in volume.
w/w	weight in weight.

Units of Measurement

The information below shows imperial to SI unit conversions for the units of measurement most commonly used in the *Handbook*. SI units are used throughout with, where appropriate, imperial units reported in parentheses.

Area
1 square inch (in^2) = 6.4516×10^{-4} square meter (m^2)
1 square foot (ft^2) = 9.29030×10^{-2} square meter (m^2)
1 square yard (yd^2) = 8.36127×10^{-1} square meter (m^2)

Density
1 pound per cubic foot (lb/ft^3) = 16.0185 kilograms per cubic meter (kg/m^3)

Energy
1 kilocalorie (kcal) = 4.1840×10^3 joules (J)

Force
1 dyne (dynes) = 1×10^{-5} newton (N)

Length
1 angstrom (ã) = 10^{-10} meter (m)
1 inch (in) = 2.54×10^{-2} meter (m)
1 foot (ft) = 3.048×10^{-1} meter (m)
1 yard (yd) = 9.144×10^{-1} meter (m)

Pressure
1 atmosphere (atm) = 0.101325 megapascal (MPa)
1 millimeter of mercury (mmHg) = 133.322 pascals (Pa)
1 pound per square inch (psi) = 6894.76 pascals (Pa)

Surface tension
1 dyne per centimeter (dyne/cm) = 1 millinewton per meter (mN/m)

Temperature
Celsius (°C) = (1.8 × °C) + 32 Fahrenheit (°F)
Fahrenheit (°F) = (0.556 × °F) –17.8 Celsius (°C)

Viscosity (dynamic)
1 centipoise (cP) = 1 millipascal second (mPa s)
1 poise (P) = 0.1 pascal second (Pa s)

Viscosity (kinematic)
1 centistoke (cSt) = 1 square millimeter per second (mm^2/s)

Volume
1 cubic inch (in^3) = 1.63871×10^{-5} cubic meter (m^3)
1 cubic foot (ft^3) = 2.83168×10^{-2} cubic meter (m^3)
1 cubic yard (yd^3) = 7.64555×10^{-1} cubic meter (m^3)
1 pint (UK) = 5.68261×10^{-4} cubic meter (m^3)
1 pint (US) = 4.73176×10^{-4} cubic meter (m^3)
1 gallon (UK) = 4.54609×10^{-3} cubic meter (m^3)
1 gallon (US) = 3.78541×10^{-3} cubic meter (m^3)

Acacia

1 Nonproprietary Names

BP: Acacia
JP: Acacia
PhEur: Acaciae gummi
USPNF: Acacia

2 Synonyms

Acacia gum; arabic gum; E414; gum acacia; gummi africanum; gum arabic; gummi arabicum; gummi mimosae; talha gum.

3 Chemical Name and CAS Registry Number

Acacia [9000-01-5]

4 Empirical Formula and Molecular Weight

Acacia is a complex, loose aggregate of sugars and hemicelluloses with a molecular weight of approximately 240 000–580 000. The aggregate consists essentially of an arabic acid nucleus to which are connected calcium, magnesium, and potassium along with the sugars arabinose, galactose, and rhamnose.

5 Structural Formula

See Section 4.

6 Functional Category

Emulsifying agent; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Acacia is mainly used in oral and topical pharmaceutical formulations as a suspending and emulsifying agent, often in combination with tragacanth. It is also used in the preparation of pastilles and lozenges, and as a tablet binder, although if used incautiously it can produce tablets with a prolonged disintegration time. Acacia has also been evaluated as a bioadhesive;(1) and has been used in novel tablet formulations,(2) and modified release tablets.(3) *See* Table I.

Acacia is also used in cosmetics, confectionery, food products, and spray-dried flavors.(4)

See also Section 18.

Table I: Uses of acacia.

Use	Concentration (%)
Emulsifying agent	10–20
Pastille base	10–30
Suspending agent	5–10
Tablet binder	1–5

8 Description

Acacia is available as white or yellowish-white thin flakes, spheroidal tears, granules, powder, or spray-dried powder. It is odorless and has a bland taste.

9 Pharmacopeial Specifications

The PhEur 2005 provides monographs on acacia and spray-dried acacia, while the USPNF 23 describes acacia in a single monograph that encompasses tears, flakes, granules, powder, and spray-dried powder. The JP 2001 also has monographs on acacia and powdered acacia. *See* Table II.

Table II: Pharmacopeial specifications for acacia.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	+	+	+
Microbial limit	—	$\leqslant 10^4$/g	+
Water	⩽17.0%	⩽15.0%	⩽15.0%
	⩽15.0%(a)	⩽10.0%(b)	—
Total ash	⩽4.0%	⩽4.0%	⩽4.0%
Acid-insoluble ash	⩽0.5%	—	⩽0.5%
Insoluble residue	⩽0.2%	⩽0.5%	⩽50 mg
Arsenic	—	—	⩽3 ppm
Lead	—	—	⩽0.001%
Heavy metals	—	—	⩽0.004%
Starch, dextrin, and agar	+	+	+
Tannin-bearing gums	+	+	+
Tragacanth	—	+	—
Sterculia gum	—	+	—
Glucose and fructose	—	+	—
Solubility and reaction	—	—	+
Organic volatile impurities	—	—	+

(a) Powdered acacia.
(b) Spray-dried acacia.

10 Typical Properties

Acidity/alkalinity: pH = 4.5–5.0 (5% w/v aqueous solution)
Acid value: 2.5
Hygroscopicity: at relative humidities of 25–65%, the equilibrium moisture content of powdered acacia at 25°C is 8–13% w/w, but at relative humidities above about 70% it absorbs substantial amounts of water.
Solubility: soluble 1 in 20 of glycerin, 1 in 20 of propylene glycol, 1 in 2.7 of water; practically insoluble in ethanol (95%). In water, acacia dissolves very slowly, although almost completely after two hours, in twice the mass of water leaving only a very small residue of powder. The solution is colorless or yellowish, viscous, adhesive, and translucent. Spray-dried acacia dissolves more rapidly, in about 20 minutes.
Specific gravity: 1.35–1.49
Viscosity (dynamic): 100 mPa s (100 cP) for a 30% w/v aqueous solution at 20°C. The viscosity of aqueous acacia solutions varies depending upon the source of the material, processing,

storage conditions, pH, and the presence of salts. Viscosity increases slowly up to about 25% w/v concentration and exhibits Newtonian behavior. Above this concentration, viscosity increases rapidly (non-Newtonian rheology). Increasing temperature or prolonged heating of solutions results in a decrease of viscosity owing to depolymerization or particle agglomeration. *See also* Section 12.

11 Stability and Storage Conditions

Aqueous solutions are subject to bacterial or enzymatic degradation but may be preserved by initially boiling the solution for a short time to inactivate any enzymes present; microwave irradiation can also be used.(5) Aqueous solutions may also be preserved by the addition of an antimicrobial preservative such as 0.1% w/v benzoic acid, 0.1% w/v sodium benzoate, or a mixture of 0.17% w/v methylparaben and 0.03% propylparaben. Powdered acacia should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Acacia is incompatible with a number of substances including amidopyrine, apomorphine, cresol, ethanol (95%), ferric salts, morphine, phenol, physostigmine, tannins, thymol, and vanillin.

An oxidizing enzyme present in acacia may affect preparations containing easily oxidizable substances. However, the enzyme may be inactivated by heating at 100°C for a short time; *see* Section 11.

Many salts reduce the viscosity of aqueous acacia solutions, while trivalent salts may initiate coagulation. Aqueous solutions carry a negative charge and will form coacervates with gelatin and other substances. In the preparation of emulsions, solutions of acacia are incompatible with soaps.

13 Method of Manufacture

Acacia is the dried gummy exudate obtained from the stems and branches of *Acacia senegal* (Linné) Willdenow or other related species of *Acacia* (Fam. Leguminosae) that grow mainly in the Sudan and Senegal regions of Africa.

The bark of the tree is incised and the exudate allowed to dry on the bark. The dried exudate is then collected, processed to remove bark, sand, and other particulate matter, and graded. Various acacia grades differing in particle size and other physical properties are thus obtained. A spray-dried powder is also commercially available.

14 Safety

Acacia is used in cosmetics, foods, and oral and topical pharmaceutical formulations. Although it is generally regarded as an essentially nontoxic material, there have been a limited number of reports of hypersensitivity to acacia after inhalation or ingestion.(6,7) Severe anaphylactic reactions have occurred following the parenteral administration of acacia and it is now no longer used for this purpose.(6)

The WHO has not set an acceptable daily intake for acacia as a food additive because the levels necessary to achieve a desired effect were not considered to represent a hazard to health.(8)

LD_{50} (hamster, oral): >18 g/kg(9)
LD_{50} (mouse, oral): >16 g/kg
LD_{50} (rabbit, oral): 8.0 g/kg
LD_{50} (rat, oral): >16 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Acacia can be irritant to the eyes and skin and upon inhalation. Gloves, eye protection, and a dust respirator are recommended.

16 Regulatory Status

GRAS listed. Accepted for use in Europe as a food additive. Included in the FDA Inactive Ingredients Guide (oral preparations and buccal or sublingual tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients. Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Ceratonia; guar gum; tragacanth.

18 Comments

Concentrated aqueous solutions are used to prepare pastilles since on drying they form solid rubbery or glasslike masses depending upon the concentration used. Foreign policy changes and politically unstable conditions in Sudan, which is the principal supplier of acacia, has created a need to find a suitable replacement.(10) Poloxamer 188 (12–15% w/w) can be used to make an oil/water emulsion with similar rheological characteristics to acacia. Other natural by-products of foods can also be used.(11) Acacia is also used in the food industry as an emulsifier, stabilizer, and thickener. A specification for acacia is contained in the Food Chemicals Codex (FCC).

The EINECS number for acacia is 232-519-5.

19 Specific References

1 Attama AA, Adiknu MV, Okoli ND. Studies on bioadhesive granules. *STP Pharma Sci* 2003; **13**(3): 177–181.
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11 I-Achi A, Greenwood R, Akin-Isijola A. Experimenting with a new emulsifying agent (tahini) in mineral oil. *Int J Pharm Compound* 2000; **4**(4): 315–317.

20 General References

Anderson DMW, Dea ICM. Recent advances in the chemistry of acacia gums. *J Soc Cosmet Chem* 1971; **22**: 61–76.

Anderson DM, Douglas DM, Morrison NA, Wang WP. Specifications for gum arabic (*Acacia Senegal*): analytical data for samples collected between 1904 and 1989. *Food Add Contam* 1990; **7**: 303–321.

Aspinal GO. Gums and mucilages. *Adv Carbohydr Chem Biochem* 1969; **24**: 333–379.

Whistler RL. *Industrial Gums*. New York: Academic Press, 1959.

21 Authors

AH Kibbe.

22 Date of Revision

20 August 2005.

Acesulfame Potassium

1 Nonproprietary Names

PhEur: Acesulfamum kalicum

2 Synonyms

Acesulfame K; E950; 6-methyl-3,4-dihydro-1,2,3-oxathiazin-4(3*H*)-one 2,2-dioxide potassium salt; *Sunett*; *Sweet One*.

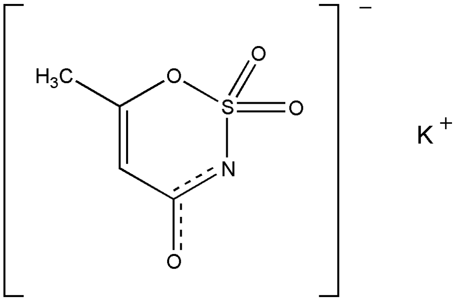
3 Chemical Name and CAS Registry Number

6-Methyl-1,2,3-oxathiazin-4(3*H*)-one-2,2-dioxide potassium salt [55589-62-3]

4 Empirical Formula and Molecular Weight

$C_4H_4KNO_4S$ 201.24

5 Structural Formula



6 Functional Category

Sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

Acesulfame potassium is used as an intense sweetening agent in cosmetics, foods, beverage products, table-top sweeteners, vitamin and pharmaceutical preparations, including powder mixes, tablets, and liquid products. It is widely used as a sugar substitute in compounded formulations,(1) and as a toothpaste sweetener.(2)

The approximate sweetening power is 180–200 times that of sucrose. It enhances flavor systems and can be used to mask some unpleasant taste characteristics.

8 Description

Acesulfame potassium occurs as a colorless to white-colored, odorless, crystalline powder with an intensely sweet taste.

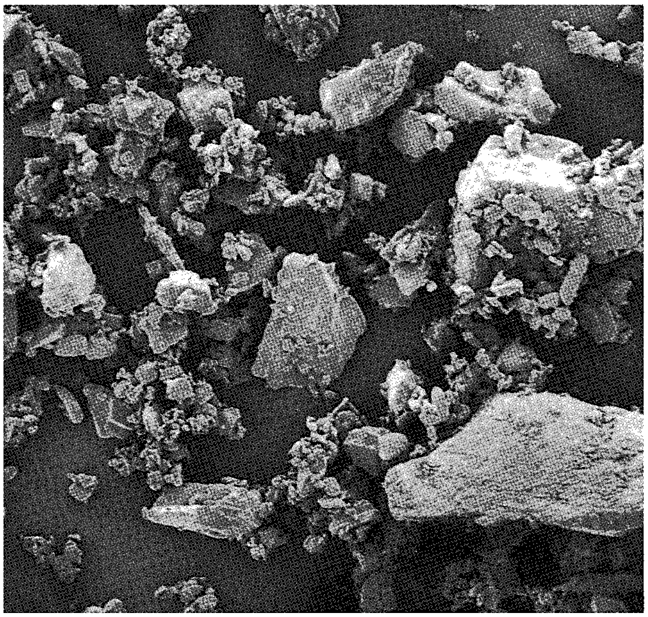
9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for acesulfame potassium.

Test	PhEur 2005
Characters	+
Identification	+
Appearance of solution	+
Acidity or alkalinity	+
Acetylacetamide	+
Impurity B and related substances	$\leqslant$20 ppm
Fluorides	$\leqslant$3 ppm
Heavy metals	$\leqslant$5 ppm
Loss on drying	$\leqslant$1.0%
Assay	99.0–101.0%

SEM: 1
Excipient: Acesulfame potassium
Magnification: 150×
Voltage: 5 kV



10 Typical Properties

Bonding index: 0.007
Brittle fracture index: 0.08(3)
Flowability: 19% (Carr compressibility index)(3)
Density (bulk): 1.04 g/cm^3(3)
Density (tapped): 1.28 g/cm^3(3)
Elastic modulus: 4000 MPa(3)
Melting point: 250°C
Solubility: *see* Table II.
Specific volume: 0.538 cm^3/g(4)
Tensile strength: 0.5 MPa(3)
Viscoelastic index: 2.6(3)

Table II: Solubility of acesulfame potassium.

Solvent	Solubility at 20°C unless otherwise stated
Ethanol	1 in 1000
Ethanol (50%)	1 in 100
Water	1 in 7.1 at 0°C
	1 in 3.7
	1 in 0.77 at 100°C

11 Stability and Storage Conditions

Acesulfame potassium possesses good stability. In the bulk form it shows no sign of decomposition at ambient temperature over many years. In aqueous solutions (pH 3.0–3.5 at 20°C) no reduction in sweetness was observed over a period of approximately 2 years. Stability at elevated temperatures is good, although some decomposition was noted following storage at 40°C for several months. Sterilization and pasteurization do not affect the taste of acesulfame potassium.(5)

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

—

13 Method of Manufacture

Acesulfame potassium is synthesized from acetoacetic acid *tert*-butyl ester and fluorosulfonyl isocyanate. The resulting compound is transformed to fluorosulfonyl acetoacetic acid amide, which is then cyclized in the presence of potassium hydroxide to form the oxathiazinone dioxide ring system. Because of the strong acidity of this compound, the potassium salt is produced directly.

An alternative synthesis route for acesulfame potassium starts with the reaction between diketene and amidosulfonic acid. In the presence of dehydrating agents, and after neutralization with potassium hydroxide, acesulfame potassium is formed.

14 Safety

Acesulfame potassium is widely used in beverages, cosmetics, foods, and pharmaceutical formulations and is generally regarded as a relatively nontoxic and nonirritant material. Pharmacokinetic studies have shown that acesulfame potassium is not metabolized and is rapidly excreted unchanged in the urine. Long-term feeding studies in rats and dogs showed no evidence to suggest acesulfame potassium is mutagenic or carcinogenic.(6)

The WHO has set an acceptable daily intake for acesulfame potassium of up to 15 mg/kg body-weight.(6)

LD_{50} (rat, IP): 2.2 g/kg(5)
LD_{50} (rat, oral): 6.9–8.0 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide for oral and sublingual preparations. Included in the Canadian List of Acceptable Non-medicinal Ingredients. Accepted for use in Europe as a food additive. It is also accepted for use in certain food products in the USA and several countries in Central and South America, the Middle East, Africa, Asia, and Australia.

17 Related Substances

Alitame.

18 Comments

The perceived intensity of sweeteners relative to sucrose depends upon their concentration, temperature of tasting, and pH, and on the flavor and texture of the product concerned.

Intense sweetening agents will not replace the bulk, textural, or preservative characteristics of sugar, if sugar is removed from a formulation.

Synergistic effects for combinations of sweeteners have been reported, e.g., acesulfame potassium with aspartame or sodium cyclamate. A ternary combination of sweeteners that includes acesulfame potassium and sodium saccharin has a greater decrease in sweetness upon repeated tasting than other combinations.(7)

Note that free acesulfame acid is not suitable for use as a sweetener.

A specification for acesulfame potassium is contained in the Food Chemicals Codex (FCC).

19 Specific References

1 Kloesel L. Sugar substitutes. *Int J Pharm Compound* 2000; **4**(2): 86–87.
2 Schmidt R, Janssen E, Haussler O, *et al*. Evaluating toothpaste sweetening. *Cosmet Toilet* 2000; **115**: 49–53.
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5 Lipinski G-WvR, Huddart BE. Acesulfame K. *Chem Ind* 1983; **11**: 427–432.
6 FAO/WHO. Evaluation of certain food additives and contaminants. Thirty-seventh report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1991; No. 806.
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20 General References

Anonymous. Artificial sweetners. *Can Pharm J* 1996; **129**: 22.
Lipinski G-WvR, Lück E. Acesulfame K: a new sweetener for oral cosmetics. *Manuf Chem* 1981; **52**(5): 37.
Marie S. Sweeteners. In: Smith J, ed. *Food Additives User's Handbook*. Glasgow: Blackie, 1991: 47–74.
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21 Authors

JH Chu.

22 Date of Revision

12 August 2005.

Acetic Acid, Glacial

1 Nonproprietary Names

BP: Glacial acetic acid
JP: Glacial acetic acid
PhEur: Acidum aceticum glaciale
USP: Glacial acetic acid

2 Synonyms

E260; ethanoic acid; ethylic acid; methane carboxylic acid; vinegar acid.

See also Sections 17 and 18.

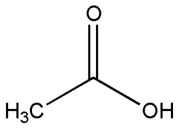
3 Chemical Name and CAS Registry Number

Ethanolic acid [64-19-7]

4 Empirical Formula and Molecular Weight

$C_2H_4O_2$ 60.05

5 Structural Formula



6 Functional Category

Acidifying agent.

7 Applications in Pharmaceutical Formulations or Technology

Glacial and diluted acetic acid solutions are widely used as acidifying agents in a variety of pharmaceutical formulations and food preparations. Acetic acid is used in pharmaceutical products as a buffer system when combined with an acetate salt such as sodium acetate. Acetic acid is also claimed to have some antibacterial and antifungal properties.

8 Description

Glacial acetic acid occurs as a crystalline mass or a clear, colorless volatile solution with a pungent odor.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for glacial acetic acid.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	+	+	—
Freezing point	⩾14.5°C	⩾14.8°C	⩾15.6°C
Nonvolatile matter	⩽1.0 mg	⩽0.01%	⩽1.0 mg
Sulfate	+	+	+
Chloride	+	+	+
Heavy metals	⩽10 ppm	⩽5 ppm	⩽5 ppm
Iron	—	⩽5 ppm	—
Readily oxidizable impurities	+	+	+
Assay	⩾99.0%	99.5–100.5%	99.5–100.5%

10 Typical Properties

Acidity/alkalinity:
pH = 2.4 (1 M aqueous solution);
pH = 2.9 (0.1 M aqueous solution);
pH = 3.4 (0.01 M aqueous solution).

Boiling point: 118°C

Dissociation constant: pK_a = 4.76

Flash point: 39°C (closed cup); 57°C (open cup).

Melting point: 17°C

Refractive index: n_D^{20} = 1.3718

Solubility: miscible with ethanol, ether, glycerin, water, and other fixed and volatile oils.

Specific gravity: 1.045

11 Stability and Storage Conditions

Acetic acid should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Acetic acid reacts with alkaline substances.

13 Method of Manufacture

Acetic acid is usually made by one of three routes: acetaldehyde oxidation, involving direct air or oxygen oxidation of liquid acetaldehyde in the presence of manganese acetate, cobalt acetate, or copper acetate; liquid-phase oxidation of butane or naphtha; methanol carbonylation using a variety of techniques.

14 Safety

Acetic acid is widely used in pharmaceutical applications primarily to adjust the pH of formulations and is thus generally regarded as relatively nontoxic and nonirritant. However, glacial acetic acid or solutions containing over 50% w/w acetic acid in water or organic solvents are considered corrosive and can cause damage to skin, eyes, nose, and mouth. If swallowed glacial acetic acid causes severe gastric irritation similar to that caused by hydrochloric acid.(1)

Dilute acetic acid solutions containing up to 10% w/w of acetic acid have been used topically following jellyfish stings.(2) Dilute acetic acid solutions containing up to 5% w/w of acetic acid have also been applied topically to treat wounds and burns infected with *Pseudomonas aeruginosa*.(3)

The lowest lethal oral dose of glacial acetic acid in humans is reported to be 1470 μg/kg.(4) The lowest lethal concentration on inhalation in humans is reported to be 816 ppm.(4) Humans, are, however, estimated to consume approximately 1 g/day of acetic acid from the diet.

LD_{50} (mouse, IV): 0.525 g/kg(4)
LD_{50} (rabbit, skin): 1.06 g/kg
LD_{50} (rat, oral): 3.31 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Acetic acid, particularly glacial acetic acid, can cause burns on contact with the skin, eyes, and mucous membranes. Splashes should be washed with copious quantities of water. Protective clothing, gloves, and eye protection are recommended.

In the UK, the occupational exposure limits for acetic acid are 25 mg/m^3 (10 ppm) long-term (8-hour TWA) and 37 mg/m^3 (15 ppm) short-term (15-minutes).(5)

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (injections, nasal, ophthalmic, and oral preparations). Included in parenteral and nonparenteral preparations licensed in the UK.

17 Related Substances

Acetic acid; artificial vinegar; dilute acetic acid.

Acetic acid

Comments: a diluted solution of glacial acetic acid containing 30–37% w/w of acetic acid. *See* Section 18.

Artificial vinegar

Comments: a solution containing 4% w/w of acetic acid.

Dilute acetic acid

Comments: a weak solution of acetic acid which may contain between 6–10% w/w of acetic acid. *See* Section 18.

18 Comments

In addition to glacial acetic acid, many pharmacopeias contain monographs for diluted acetic acid solutions of various strengths. For example, the USPNF 23 has a monograph for acetic acid, which is defined as an acetic acid solution containing 36.0–37.0% w/w of acetic acid. Similarly, the BP 2004 contains separate monographs for glacial acetic acid, acetic acid (33%), and acetic acid (6%). Acetic acid (33%) BP 2004 contains 32.5–33.5% w/w of acetic acid. Acetic acid (6%) BP 2004 contains 5.7–6.3% w/w of acetic acid. The JP 2001 also contains a monograph for acetic acid that specifies that it contains 30.0–32.0% w/w of acetic acid.

A specification for glacial acetic acid is contained in the Food Chemicals Codex (FCC).

The EINECS number for acetic acid is 200-580-7.

19 Specific References

1 Sweetman SC, ed. *Martindale: The Complete Drug Reference*, 34th edn. London: Pharmaceutical Press, 2005: 1645.
2 Fenner PJ, Williamson JA. Worldwide deaths and severe envenomation from jellyfish stings. *Med J Aust* 1996; **165**: 658–661.
3 Milner SM. Acetic acid to treat *Pseudomonas aeruginosa* in superficial wounds and burns. *Lancet* 1992; **340**: 61.
4 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials,* 11th edn. New York: Wiley, 2004: 15–16.
5 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*, Sudbury: Health and Safety Executive, 2002.

20 General References

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21 Authors

WG Chambliss.

22 Date of Revision

8 August 2005.

Acetone

1 Nonproprietary Names

BP: Acetone
PhEur: Acetonum
USPNF: Acetone

2 Synonyms

Dimethylformaldehyde; dimethyl ketone; β-ketopropane; pyroacetic ether.

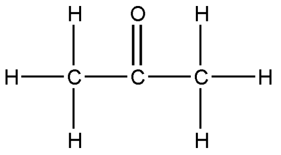
3 Chemical Name and CAS Registry Number

2-Propanone [67-64-1]

4 Empirical Formula and Molecular Weight

C_3H_6O 58.08

5 Structural Formula



6 Functional Category

Solvent.

7 Applications in Pharmaceutical Formulation or Technology

Acetone is used as a solvent or cosolvent in topical preparations, and as an aid in wet granulation.(1,2) It has also been used when formulating tablets with water-sensitive active ingredients, or to solvate poorly water-soluble binders in a wet granulation process. Acetone has also been used in the formulation of microspheres to enhance drug release.(3) Owing to its low boiling point, acetone has been used to extract thermolabile substances from crude drugs.(4)

8 Description

Acetone is a colorless volatile, flammable, transparent liquid, with a sweetish odor and pungent sweetish taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for acetone.

Test	PhEur 2005 (Suppl. 5.1)	USPNF 23
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Acidity or alkalinity	+	—
Relative density	0.790–0.793	⩽0.789
Related substances	+	—
Matter insoluble in water	+	—
Reducing substances	+	+
Residue on evaporation	⩽50 ppm	⩽0.004%
Water	⩽3 g/L	+
Assay	—	⩾99.0%

10 Typical Properties

Boiling point: 56.2°C
Flash point: –20°C
Melting point: 94.3°C
Refractive index: $n_D^{20} = 1.359$
Solubility: soluble in water; freely soluble in ethanol (95%)
Vapor pressure: 185 mmHg at 20°C

11 Stability and Storage Conditions

Acetone should be stored in a cool, dry, well-ventilated place out of direct sunlight.

12 Incompatibilities

Acetone reacts violently with oxidizing agents, chlorinated solvents, and alkali mixtures. It reacts vigorously with sulfur dichloride, potassium *t*-butoxide, and hexachloromelamine. Acetone should not be used as a solvent for iodine, as it forms a volatile compound that is extremely irritating to the eyes.(4)

13 Method of Manufacture

Acetone is obtained by fermentation as a by-product of *n*-butyl alcohol manufacture, or by chemical synthesis from isopropyl alcohol; from cumene as a by-product in phenol manufacture; or from propane as a by-product of oxidation-cracking.

14 Safety

Acetone is considered moderately toxic, and is a skin irritant and severe eye irritant. Skin irritation has been reported due to its defatting action, and prolonged inhalation may result in headaches. Inhalation of acetone can produce systemic effects such as conjunctival irritation, respiratory system effects, nausea, and vomiting.(5)

LD_{50} (mouse, oral): 3.0 g/kg(5)
LD_{50} (mouse, IP): 1.297 g/kg
LD_{50} (rabbit, oral): 5.340 g/kg
LD_{50} (rabbit, skin): 0.2 g/kg

LD_{50} (rat, IV): 5.5 g/kg
LD_{50} (rat, oral): 5.8 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Acetone is a skin and eye irritant (*see* Section 14), therefore gloves, eye protection and a respirator are recommended. In the UK, the long-term (8-hour TWA) exposure limit for acetone is 1210 mg/m^3 (500 ppm). The short-term (15-minute) exposure limit is 3620 mg/m^3 (1500 ppm).(6)

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (inhalation solution; oral tablets; topical preparations). Included in the Canadian List of Acceptable Non-medicinal Ingredients. Included in nonparenteral medicines licensed in the UK.

17 Related Substances

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18 Comments

A specification for acetone is included in the Japanese Pharmaceutical Excipients (JPE).(7) The EINECS number for acetone is 200-662-2.

19 Specific References

1 Ash M, Ash I. *Handbook of Pharmaceutical Additives*, 2nd edn. Endicott, NY: Synapse Information Resources, 2002: 282.
2 Tang ZG, Black RA, Curran JM, *et al.* Surface properties and biocompatibility of solvent-cast poly[ε-caprolactone] films. *Biomaterials* 2004; **25**(19): 4741–4748.
3 Ruan G, Feng SS. Preparation and characterization of poly(lactic acid)–poly(ethylene glycol)–poly(lactic acid) (PLA-PEG-PLA) microspheres for controlled release of paclitaxel. *Biomaterials* 2003; **24**(27): 5037–5044.
4 Todd RG, Wade A, eds. *The Pharmaceutical Codex*, 11th edn. London: Pharmaceutical Press, 1979: 6.
5 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 22–23.
6 Health and Safety Executive: *EH40/2002: Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.
7 Japan Pharmaceutical Excipients Council. *Japanese Pharmaceutical Excipients 2004*. Tokyo: Yakuji Nippo, 2004: 35–36.

20 General References

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21 Authors

AH Kibbe, SC Owen.

22 Date of Revision

23 August 2005.

Acetyltributyl Citrate

1 Nonproprietary Names

USPNF: Acetyltributyl citrate
PhEur: Tributylis acetylcitras

2 Synonyms

Acetylbutyl citrate; acetylcitric acid, tributyl ester; ATBC; *Citroflex A-4*; tributyl acetylcitrate; tributyl *O*-acetylcitrate; tributyl citrate acetate.

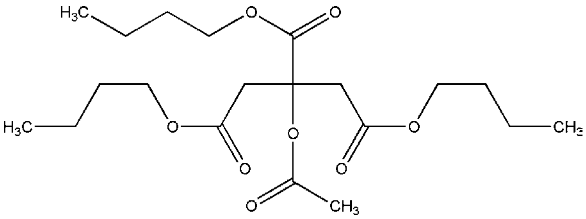
3 Chemical Name and CAS Registry Number

1,2,3-Propanetricarboxylic acid, 2-acetyloxy, tributyl ester [77-90-7]

4 Empirical Formula and Molecular Weight

$C_{20}H_{34}O_8$ 402.5

5 Structural Formula



6 Functional Category

Plasticizer.

7 Applications in Pharmaceutical Formulation or Technology

Acetyltributyl citrate is used to plasticize polymers in formulated pharmaceutical coatings,(1–5) including capsules, tablets, beads, and granules for taste masking, immediate release, sustained-release and enteric formulations.

8 Description

Acetyltributyl citrate is a clear, odorless, practically colorless, oily liquid.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for acetyltributyl citrate.

Test	PhEur 2005	USPNF 23
Identification	+	+
Appearance	—	+
Characters	—	+
Specific gravity	1.045–1055	—
Refractive index	1.4410–1.4425	1.442–1.445
Sulfated ash	—	⩽0.10%
Acidity	+	+
Water	⩽0.25%	⩽0.25%
Heavy metals	⩽0.001%	⩽0.001%
Assay (anhydrous basis)	⩾99.0%	99.0–101.0%

10 Typical Properties

Acid value: 0.02
Boiling point: 326°C (decomposes)
Flash point: 204°C
Pour point: −59°C
Solubility: miscible with acetone, ethanol, and vegetable oil; practically insoluble in water.
Viscosity (dynamic): 33 mPa s (33 cP) at 25°C

11 Stability and Storage Conditions

Acetyltributyl citrate should be stored in a well-closed container in a cool, dry location at temperatures not exceeding 38°C. When stored in accordance with these conditions, acetyltributyl citrate is a stable product.

12 Incompatibilities

Acetyltributyl citrate is incompatible with strong alkalis and oxidizing materials.

13 Method of Manufacture

Acetyltributyl citrate is prepared by the esterification of citric acid with butanol followed by acylation with acetic anhydride.

14 Safety

Acetyltributyl citrate is used in oral pharmaceutical formulations and films intended for direct food contact. It is also used in self-adhesive thin films used for topical delivery systems.(6) It is generally regarded as a relatively nontoxic and nonirritating material. However, ingestion of large quantities may be harmful.

LD_{50} (cat, oral): >50 mL/kg(7)
LD_{50} (mouse, IP): >4 g/kg
LD_{50} (rat, oral): >31.5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Acetyltributyl citrate is slightly irritating to the eyes and may be irritating to the respiratory system as a mist or at elevated temperatures. Gloves and eye protection are recommended for normal handling, and a respirator is recommended when using acetyltributyl citrate at elevated temperatures.

16 Regulatory Status

Included in FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Approved in the USA for direct food contact in food films.

17 Related Substances

Acetyltriethyl citrate; tributyl citrate; triethyl citrate.

18 Comments

Acetyltributyl citrate is used as a plasticizer in food contact films, although it has been known to migrate from food-grade PVC films into high-fat foods such as olive oil.(8)

Polylactide plasticized with acetyltributyl citrate has been investigated as a biodegradable barrier for use in guided-tissue regeneration therapy.(9)

The EINECS number for acetyltributyl citrate is 201-067-0.

19 Specific References

1 Gutierrez-Rocca JC, McGinity JW. Influence of water soluble and insoluble plasticizer on the physical and mechanical properties of acrylic resin copolymers. *Int J Pharm* 1994; **103**: 293–301.

2 Lehmann K. Chemistry and application properties of polymethacrylate coating systems. In: McGinity JW, ed. *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*. New York: Marcel Dekker, 1989: 153–245.

3 Steurnagel CR. Latex emulsions for controlled drug delivery. In: McGinity JW, ed. *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*. New York: Marcel Dekker, 1989: 1–61.

4 Gutierrez-Rocca JC, McGinity JW. Influence of aging on the physical-mechanical properties of acrylic resin films cast from aqueous dispersions and organic solutions. *Drug Dev Ind Pharm* 1993; **19**(3): 315–332.

5 Repka MA, Gerding TG, Repka SL. Influence of plasticisers and drugs on the physical-mechanical properties of hydroxypropylcellulose films prepared by hot melt extrusion. *Drug Dev Ind Pharm* 1999; **25**(5): 625–633.

6 Lieb S, Szeimies RM, Lee G. Self-adhesive thin films for topical delivery of 5-aminolevulinic acid. *Eur J Pharm Biopharm* 2002; **53**(1): 99–106.

7 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials,* 11th edn. New York: Wiley, 2004: 3512.

8 Goulas AE, Riganakos KA, Ehlermann DA, *et al*. Effect of high-dose electron beam irradiation on the migration of DOA and ATBC plasticizers from food-grade PVC and PVDC/PVC films, respectively, into olive oil. *J Food Prot* 1998; **61**(6): 720–724.

9 Dorfer CE, Kim TS, Steinbrenner H, *et al*. Regenerative periodontal surgery in interproximal intrabony defects with biodegradable barriers. *J Clin Peridontol* 2000; **27**(3): 162–168.

20 General References

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21 Authors

SW Kennedy.

22 Date of Revision

15 August 2005.

Acetyltriethyl Citrate

1 Nonproprietary Names

USPNF: Acetyltriethyl citrate

2 Synonyms

ATEC; *Citroflex A-2*; triethyl acetylcitrate; triethyl *O*-acetylcitrate; triethyl citrate acetate.

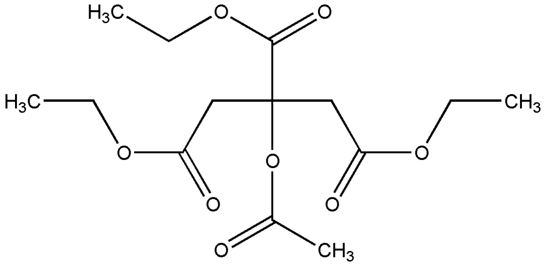
3 Chemical Name and CAS Registry Number

1,2,3-Propanetricarboxylic acid, 2-acetyloxy, triethyl ester [77-89-4]

4 Empirical Formula and Molecular Weight

$C_{14}H_{22}O_8$ 318.3

5 Structural Formula



6 Functional Category

Plasticizer.

7 Applications in Pharmaceutical Formulation or Technology

Acetyltriethyl citrate is used to plasticize polymers in formulated pharmaceutical coatings.(1) The coating applications include capsules, tablets, beads and granules for taste masking, immediate release, sustained-release and enteric formulations.(2–5) It is also used in diffusion-controlled release drug delivery systems.(6)

8 Description

Acetyltriethyl citrate occurs as a clear, odorless, practically colorless oily liquid.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for acetyltriethyl citrate.

Test	USPNF 23
Identification	+
Specific gravity	1.135–1.139
Refractive index	1.432–1.441
Acidity	+
Water	⩽0.3%
Heavy metals	⩽0.001%
Assay (anhydrous basis)	⩾99.0%

10 Typical Properties

Acid value: 0.02
Boiling point: 294°C (decomposes)
Flash point: 188°C
Pour point: −43°C
Solubility: soluble 1 in 140 of water; miscible with acetone, ethanol, and propan-2-ol.
Viscosity (dynamic): 54 mPa s (54 cP) at 25°C.

11 Stability and Storage Conditions

Acetyltriethyl citrate should be stored in dry, closed containers at temperatures not exceeding 38°C. When stored in accordance with these conditions, acetyltriethyl citrate is a stable product.

12 Incompatibilities

Acetyltriethyl citrate is incompatible with strong alkalis and oxidizing materials.

13 Method of Manufacture

Acetyltriethyl citrate is prepared by the esterification of citric acid with ethanol followed by acylation with acetic anhydride.

14 Safety

Acetyltriethyl citrate is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritating material. However, ingestion of large quantities may be harmful.

LD_{50} (cat, oral): 8.5 g/kg(7)
LD_{50} (mouse, IP): 1.15 g/kg
LD_{50} (rat, oral): 7 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Acetyltriethyl citrate may be irritating to the eyes or the respiratory system as a mist or at elevated temperatures. Gloves and eye protection are recommended for normal handling and a respirator is recommended if used at elevated temperatures.

16 Regulatory Status

Approved in the USA for direct food contact in food films.

17 Related Substances

Acetyltributyl citrate; tributyl citrate; triethyl citrate.

18 Comments

The EINECS number for acetyltriethyl citrate is 201-066-5.

19 Specific References

1 Jensen JL, Appel LE, Clair JH, Zentner GM. Variables that affect the mechanism of drug release from osmotic pumps coated with acrylate/methacrylate copolymer latexes. *J Pharm Sci* 1995; **84**: 530–533.

2 Gutierrez-Rocca JC, McGinity JW. Influence of water soluble and insoluble plasticizer on the physical and mechanical properties of acrylic resin copolymers. *Int J Pharm* 1994; **103**: 293–301.

3 Lehmann K. Chemistry and application properties of polymethacrylate coating systems. In: McGinity JW, ed. *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*. New York: Marcel Dekker, 1989: 153–245.

4 Steurnagel CR. Latex emulsions for controlled drug delivery. In: McGinity JW, ed. *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*. New York: Marcel Dekker, 1989: 1–61.

5 Gutierrez-Rocca JC, McGinity JW. Influence of aging on the physical-mechanical properties of acrylic resin films cast from aqueous dispersions and organic solutions. *Drug Dev Ind Pharm* 1993; **19**(3): 315–332.

6 Siepmann J, Lecomte F, Bodmeier R. Diffusion-controlled drug delivery systems: calculation of the required composition to achieve desired release profiles. *J Control Release* 1999; **60**(2–3): 379–389.

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20 General References

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21 Authors

SW Kennedy.

22 Date of Revision

15 August 2005.

Agar

1 Nonproprietary Names

JP: Agar
PhEur: Agar
USPNF: Agar

2 Synonyms

Agar-agar; Bengal isinglass; Ceylon isinglass; Chinese isinglass; E406; gelosa; gelose; Japan agar; Japan isinglass; layor carang.

3 Chemical Name and CAS Registry Number

Agar [9002-18-0]

4 Empirical Formula and Molecular Weight

See Section 5.

5 Structural Formula

Agar is a dried, hydrophilic, colloidal polysaccharide complex extracted from the agarocytes of algae of the Rhodophyceae. The structure is believed to be a complex range of polysaccharide chains having alternating α-(1→3) and β-(1→4) linkages. There are three extremes of structure noted: namely neutral agarose; pyruvated agarose having little sulfation; and a sulfated galactan. Agar can be separated into a natural gelling fraction, agarose, and a sulfated nongelling fraction, agaropectin.

6 Functional Category

Emulsifying agent; stabilizing agent; suppository base; suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Agar is widely used in food applications as a stabilizing agent. In pharmaceutical applications, agar is used in a handful of oral tablet and topical formulations. It has also been investigated in a number of experimental pharmaceutical applications including as a sustained-release agent in gels, beads, microspheres, and tablets.(1–4) It has also been reported to work as a disintegrant in tablets.(5) Agar has been used in a floating controlled-release tablet; the buoyancy in part being attributed to air entrapped in the agar gel network.(6) It can be used as a viscosity-increasing agent in aqueous systems. Agar can also be used as a base for nonmelting, and nondisintegrating suppositories.(7) Agar has an application as a suspending agent in pharmaceutical suspensions.(8)

8 Description

Agar occurs as transparent, odorless, tasteless strips or as a coarse or fine powder. It may be weak yellowish-orange, yellowish-gray to pale-yellow colored, or colorless. Agar is tough when damp, brittle when dry.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for agar.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	+	+	—
Swelling index	—	+	—
Arsenic	—	—	⩽3 ppm
Lead	—	—	⩽0.001%
Sulfuric acid	+	—	—
Sulfurous acid and starch	+	—	—
Gelatin	—	+	+
Heavy metals	—	—	⩽0.004%
Insoluble matter	⩽15.0 mg	—	⩽15.0 mg
Water absorption	⩽75 mL	—	⩽75 mL
Loss on drying	⩽22.0%	⩽20.0%	⩽20.0%
Microbial contamination	—	⩽1000/g(a)	+
Total ash	⩽4.5%	⩽5.0%	⩽6.5%
Acid-insoluble ash	⩽0.5%	⩽1.0%	⩽0.5%
Foreign organic matter	—	—	⩽1.0%
Limit of foreign starch	—	—	+
Organic volatile impurities	—	—	+

(a) Total viable aerobic count, determined by plate-count.

10 Typical Properties

Solubility: soluble in boiling water to form a viscous solution; practically insoluble in ethanol (95%), and cold water. A 1% w/v aqueous solution forms a stiff jelly on cooling.

11 Stability and Storage Conditions

Agar solutions are most stable at pH 4–10.

Agar should be stored in a cool, dry, place. Containers of this material may be hazardous when empty since they retain product residues (dust, solids).

12 Incompatibilities

Agar is incompatible with strong oxidizing agents. Agar is dehydrated and precipitated from solution by ethanol (95%). Tannic acid causes precipitation; electrolytes cause partial dehydration and decrease in viscosity of sols.(9)

13 Method of Manufacture

Agar is obtained by freeze-drying a mucilage derived from *Gelidium amansii* Lamouroux, other species of the same family (Gelidiaceae), or other red algae (Rhodophyta).

14 Safety

Agar is widely used in food applications and has been used in oral and topical pharmaceutical applications. It is generally regarded as relatively nontoxic and nonirritant when used as an excipient.

LD_{50} (hamster, oral): 6.1 g/kg(10)
LD_{50} (mouse, oral): 16.0 g/kg
LD_{50} (rabbit, oral): 5.8 g/kg
LD_{50} (rat, oral): 11.0 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled. When heated to decomposition, agar emits acrid smoke and fumes.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients. Included in nonparenteral medicines licensed in the UK.

17 Related Substances

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18 Comments

The EINECS number for agar is 232-658-1.

19 Specific References

1 Bhardwaj TJ, Kanwar M, Lal R, Gupta A. Natural gums and modified natural gums as sustained release carriers. *Drug Dev Ind Pharm* 2000; **26**(10): 1025–1038.
2 Sakr FM, El-Said Y, El-Helw A. Design and evaluation of a dry solidification technique for preparing pharmaceutical beads. *STP Pharma Sci* 1995; **5**(4): 291–295.
3 Boraie NA, Naggar VF. Sustained release of theophylline and aminophylline from agar tablets. *Acta Pharm Jugosl* 1984; **34**(Oct–Dec): 247–256.
4 Nakano M, Nakamura Y, Takikawa K, *et al*. Sustained release of sulfamethizole from agar beads. *J Pharm Pharmacol* 1979; **31**: 869–872.
5 Fassihi AR. Characteristics of hydrogel as disintegrant in solid dose technology. *J Pharm Pharmacol* 1989; **54**: 59–62.
6 Desai S, Boston S. A floating controlled-release drug delivery system: *in vitro–in vivo* evaluation. *Pharm Res* 1993; **10**: 1321–1325.
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8 Kahela P, Hurmerinta T, Elfving R. Effect of suspending agents on the bioavailability of erythromycin ethylsuccinate mixtures. *Drug Dev Ind Pharm* 1978; **4**(3): 261–274.
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10 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 90–91.

20 General References

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21 Authors

VK Gupta.

22 Date of Revision

10 May 2005.

Albumin

1 Nonproprietary Names

BP: Human albumin solution
PhEur: Albumini humani solutio
USP: Albumin human

2 Synonyms

Albuconn; albumin human solution; *Albuminar*; *Albumisol*; *Albuspan*; *Albutein*; *Buminate*; human serum albumin; normal human serum albumin; *Plasbumin*; plasma albumin; *Pro-Bumin*; *Proserum*.

3 Chemical Name and CAS Registry Number

Serum albumin [9048-49-1]

4 Empirical Formula and Molecular Weight

Human serum albumin has a molecular weight of about 66 500 and is a single polypeptide chain consisting of 585 amino acids. Characteristic features are a single tryptophan residue, a relatively low content of methionine (6 residues), and a large number of cysteine (17) and of charged amino acid residues of aspartic acid (36), glutamic acid (61), lysine (59), and arginine (23).

5 Structural Formula

Primary structure: human albumin is a single polypeptide chain of 585 amino acids and contains seven disulfide bridges.

Secondary structure: human albumin is known to have a secondary structure that is about 55% α-helix. The remaining 45% is believed to be divided among turns, disordered, and β structures.$^{(1)}$

Albumin is the only major plasma protein that does not contain carbohydrate constituents. Assays of crystalline albumin show less than one sugar residue per molecule.

6 Functional Category

Stabilizing agent; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Albumin is primarily used as an excipient in parenteral pharmaceutical formulations, where it is used as a stabilizing agent for formulations containing proteins and enzymes.$^{(2)}$ Albumin has also been used to prepare microspheres and microcapsules for experimental drug-delivery systems.$^{(3)}$

As a stabilizing agent, albumin has been employed in protein formulations at concentrations as low as 0.003%, although concentrations of 1–5% are commonly used. Albumin has also been used as a cosolvent$^{(4)}$ for parenteral drugs, as a cryoprotectant during lyophilization, and to prevent adsorption of other proteins to surfaces.

Therapeutically, albumin solutions have been used parenterally for plasma volume replacement and to treat severe acute albumin loss. However, the benefits of using albumin in such applications in critically ill patients has been questioned.$^{(5)}$

8 Description

The USP 28 describes albumin human as a sterile nonpyrogenic preparation of serum albumin obtained from healthy human donors; *see* Section 13. It is available as a solution containing 4, 5, 20, or 25 g of serum albumin in 100 mL of solution, with not less than 96% of the total protein content as albumin. The solution contains no added antimicrobial preservative but may contain sodium acetyltryptophanate with or without sodium caprylate as a stablizing agent.

The PhEur 2005 similarly describes albumin solution as an aqueous solution of protein obtained from human plasma; *see* Section 13. It is available as a concentrated solution containing 150–250 g/L of total protein or as an isotonic solution containing 35–50 g/L of total protein. Not less than 95% of the total protein content is albumin. A suitable stabilizer against the effects of heat, such as sodium caprylate (sodium octanoate) or *N*-acetyltryptophan or a combination of these two at a suitable concentration, may be added, but no antimicrobial preservative is added.

Aqueous albumin solutions are slightly viscous and range in color from almost colorless to amber depending upon the protein concentration. In the solid state, albumin appears as brownish amorphous lumps, scales, or powder.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for albumin.

Test	PhEur 2005	USP 28
Identification	+	—
Characters	+	—
pH (10 g/L solution)	6.7–7.3	+
Polymers and aggregates	+	—
Potassium	⩽0.05 mmol/g	—
Sodium	⩽160 mmol/L	130–160 mEq/L
Heme	+	+
Aluminum	⩽200 μg/L	—
Sterility	+	+
Hepatitis B surface antigen	—	+
Pyrogens	+	+
Total protein	95–105%	⩾96%
for 4 g in 100 mL	—	93.75–106.25%
for 5 to 25 g in 100 mL	—	94.0–106.0%
Protein composition	+	—
Prekallikrein activator	⩽35 IU/mL	—

10 Typical Properties

Acidity/alkalinity: pH = 6.7–7.3 for a 1% w/v solution, in 0.9% w/v sodium chloride solution, at 20°C.

Osmolarity: a 4–5% w/v aqueous solution is isoosmotic with serum.

Solubility: freely soluble in dilute salt solutions and water. Aqueous solutions containing 40% w/v albumin can be readily prepared at pH 7.4. The high net charge of the peptide contributes to its solubility in aqueous media. The seven disulfide bridges contribute to its chemical and spatial conformation. At physiological pH, albumin has a net electrostatic charge of about –17. Aqueous albumin solutions are slightly viscous and range in color from almost colorless to amber depending on the protein concentration.

11 Stability and Storage Conditions

Albumin is a protein and is therefore susceptible to chemical degradation and denaturation by exposure to extremes of pH, high salt concentrations, heat, enzymes, organic solvents, and other chemical agents.

Albumin solutions should be protected from light and stored at a temperature of 2–25°C or as indicated on the label.

12 Incompatibilities

See Section 11.

13 Method of Manufacture

Albumin human (USP 28) Albumin human is a sterile nonpyrogenic preparation of serum albumin that is obtained by fractionating material (source blood, plasma, serum, or placentas) from healthy human donors. The source material is tested for the absence of hepatitis B surface antigen. It is made by a process that yields a product safe for intravenous use.

Albumin solution, human (PhEur 2005) Human albumin solution is an aqueous solution of protein obtained from plasma. Separation of the albumin is carried out under controlled conditions so that the final product contains not less than 95% albumin. Human albumin solution is prepared as a concentrated solution containing 150–250 g/L of total protein or as an isotonic solution containing 35–50 g/L of total protein. A suitable stabilizer against the effects of heat such as sodium caprylate (sodium octanoate) or *N*-acetyltryptophan or a combination of these two at a suitable concentration, may be added, but no antimicrobial preservative is added at any stage during preparation. The solution is passed through a bacteria-retentive filter and distributed aseptically into sterile containers, which are then closed so as to prevent contamination. The solution in its final container is heated to 60 ± 1.0°C and maintained at this temperature for not less than 10 hours. The containers are then incubated at 30–32°C for not less than 14 days or at 20–25°C for not less than 4 weeks and examined visually for evidence of microbial contamination.

14 Safety

Albumin occurs naturally in the body, comprising about 60% of all the plasma proteins. As an excipient, albumin is used primarily in parenteral formulations and is generally regarded as an essentially nontoxic and nonirritant material. Adverse reactions to albumin infusion rarely occur but include nausea, vomiting, increased salivation, chills, and febrile reactions. Urticaria and skin rash have been reported. Allergic reactions, including anaphylactic shock, can occur. Albumin infusions are contraindicated in patients with severe anemia or cardiac failure. Albumin solutions with aluminum content of less than 200 μg/L should be used in dialysis patients and premature infants.(6)

LD_{50} (monkey, IV): >12.5 g/kg(7)
LD_{50} (rat, IV): >12.5 g/kg

15 Handling Precautions

Observe handling precautions appropriate for a biologically derived blood product.

16 Regulatory Acceptance

Included in the FDA Inactive Ingredients Guide (oral, tablets, film-coatings; IV injections). Included in parenteral products licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Albumins derived from animal sources are also commercially available, e.g., bovine serum albumin.

18 Comments

A 100 mL aqueous solution of albumin containing 25 g of serum albumin is osmotically equivalent to 500 mL of normal human plasma. The EINECS number for albumin is 310-127-6.

19 Specific References

1 Bramanti E, Benedetti E. Determination of the secondary structure of isomeric forms of human serum albumin by a particular frequency deconvolution procedure applied to Fourier transform IR analysis. *Biopolymers* 1996; **38**(5): 639–653.
2 Wang JUC, Hanson MA. Parenteral formulations of proteins and peptides: stability and stabilizers. *J Parenter Sci Technol* 1988; **42**(S): S1–S26.
3 Arshady R. Albumin microspheres and microcapsules: methodology of manufacturing techniques. *J Control Release* 1990; **14**: 111–131.
4 Olson WP, Faith MR. Human serum albumin as a cosolvent for parenteral drugs. *J Parenter Sci Technol* 1988; **42**: 82–85.
5 Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *Br Med J* 1998; **317**: 235–240.
6 Quagliaro DA, Geraci VA, Dwan RE, *et al*. Aluminum in albumin for injection. *J Parenter Sci Technol* 1988; **42**: 187–190.
7 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 1970.

20 General References

Kragh-Hansen U. Structure and ligand properties of human serum albumin. *Danish Med Bull* 1990; **37**(1): 57–84.

Putnam FW, ed. *The Plasma Proteins, Structure, Function and Genetic Control*. London: Academic Press, 1975.

21 Authors

RT Guest.

22 Date of Revision

23 August 2005.

Alcohol

1 Nonproprietary Names

BP: Ethanol (96%)
JP: Ethanol
PhEur: Ethanolum (96 per centum)
USP: Alcohol

2 Synonyms

Ethyl alcohol; ethyl hydroxide; grain alcohol; methyl carbinol.

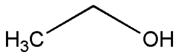
3 Chemical Name and CAS Registry Number

Ethanol [64-17-5]

4 Empirical Formula and Molecular Weight

C_2H_6O 46.07

5 Structural Formula



6 Functional Category

Antimicrobial preservative; disinfectant; skin penetrant; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Ethanol and aqueous ethanol solutions of various concentrations (*see* Sections 8 and 17) are widely used in pharmaceutical formulations and cosmetics; *see* Table I. Although ethanol is primarily used as a solvent, it is also employed in solutions as an antimicrobial preservative.(1,2) Topical ethanol solutions are also used as penetration enhancers(3–6) and as disinfectants. Ethanol has also been used in transdermal preparations in combination with *Labrasol* as a co-surfactant.(7)

Table I: Uses of alcohol.

Use	Concentration (% v/v)
Antimicrobial preservative	⩾10
Disinfectant	60–90
Extracting solvent in galenical manufacture	Up to 85
Solvent in film coating	Variable
Solvent in injectable solutions	Variable
Solvent in oral liquids	Variable
Solvent in topical products	60–90

8 Description

In the BP 2004, the term ‘ethanol’ used without other qualification refers to ethanol containing ⩾99.5% v/v of C_2H_6O. The term ‘alcohol’, without other qualification, refers to ethanol 95.1–96.9% v/v. Where other strengths are intended, the term ‘alcohol’ or ‘ethanol’ is used, followed by the statement of the strength.

In the PhEur 2005, anhydrous ethanol contains not less than 99.5% v/v of C_2H_6O at 20°C. The term ethanol (96%) is used to describe the material containing water and 95.1–96.9% v/v of C_2H_6O at 20°C.

In the USP 28, the term ‘dehydrated alcohol’ refers to ethanol ⩾99.5% v/v. The term ‘alcohol’ without other qualification refers to ethanol 94.9–96.0% v/v.

In the JP 2001, ethanol (alcohol) contains 95.1–95.6% v/v (by specific gravity) of C_2H_6O at 15°C.

In the *Handbook of Pharmaceutical Excipients,* the term ‘alcohol’ is used for either ethanol 95% v/v or ethanol 96% v/v.

Alcohol is a clear, colorless, mobile, and volatile liquid with a slight, characteristic odor and burning taste.

See also Section 17.

9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Antimicrobial activity: ethanol is bactericidal in aqueous mixtures at concentrations between 60% and 95% v/v; the optimum concentration is generally considered to be 70% v/v. Antimicrobial activity is enhanced in the presence of edetic acid or edetate salts.(1) Ethanol is inactivated in the presence of nonionic surfactants and is ineffective against bacterial spores.

Boiling point: 78.15°C

Flammability: readily flammable, burning with a blue, smokeless flame.

Flash point: 14°C (closed cup)

Solubility: miscible with chloroform, ether, glycerin, and water (with rise of temperature and contraction of volume).

Specific gravity: 0.8119–0.8139 at 20°C

Note: the above typical properties are for alcohol (ethanol 95% or 96% v/v). *See* Section 17 for typical properties of dehydrated alcohol.

11 Stability and Storage Conditions

Aqueous ethanol solutions may be sterilized by autoclaving or by filtration and should be stored in airtight containers, in a cool place.

12 Incompatibilities

In acidic conditions, ethanol solutions may react vigorously with oxidizing materials. Mixtures with alkali may darken in color owing to a reaction with residual amounts of aldehyde. Organic salts or acacia may be precipitated from aqueous solutions or dispersions. Ethanol solutions are also incompatible with aluminum containers and may interact with some drugs.

Table II: Pharmacopeial specifications for alcohol.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	+	+	—
Specific gravity	0.814–0.816	0.805–0.812	0.812–0.816
Acidity or alkalinity	+	+	+
Clarity of solution	+	+	—
Nonvolatile residue	≤1 mg/40 mL	≤25 ppm	≤1 mg/40 mL
Water-insoluble substances	—	—	+
Volatile impurities	+	+	—
Aldehydes	+	≤10 ppm v/v	+
Amyl alcohol, etc.	—	—	+
Absorbance	—	+	—
at 240 nm	—	≤ 0.40	—
at 250–260 nm	—	≤ 0.30	—
at 270–340 nm	—	≤ 0.10	—
Fusel oil constituents	+	—	—
Acetone and propan-2-ol	—	—	+
Methanol	—	≤ 200 ppm	+
Benzene	—	≤ 2 ppm	—
Acetaldehyde and acetal	—	≤ 10 ppm	—
Reducing substances	+	—	—
Organic volatile impurities	—	—	+
Chloride	+	—	—
Heavy metals	≤1.2 ppm	—	—
Assay	95.1–95.6%	95.1–96.9%	92.3–93.8% by weight 94.9–96.0% by volume

13 Method of Manufacture

Ethanol is manufactured by the controlled enzymatic fermentation of starch, sugar, or other carbohydrates. A fermented liquid is produced containing about 15% ethanol; ethanol 95% v/v is then obtained by fractional distillation. Ethanol may also be prepared by a number of synthetic methods.

14 Safety

Ethanol and aqueous ethanol solutions are widely used in a variety of pharmaceutical formulations and cosmetics. It is also consumed in alcoholic beverages.

Ethanol is rapidly absorbed from the gastrointestinal tract and the vapor may be absorbed through the lungs; it is metabolized, mainly in the liver, to acetaldehyde, which is further oxidized to acetate.

Ethanol is a central nervous system depressant and ingestion of low to moderate quantities can lead to symptoms of intoxication including muscle incoordination, visual impairment, slurred speech, etc. Ingestion of higher concentrations may cause depression of medullary action, lethargy, amnesia, hypothermia, hypoglycemia, stupor, coma, respiratory depression, and cardiovascular collapse. The lethal human blood-alcohol concentration is generally estimated to be 400–500 mg/100 mL.

Although symptoms of ethanol intoxication are usually encountered following deliberate consumption of ethanol-containing beverages, many pharmaceutical products contain ethanol as a solvent, which, if ingested in sufficiently large quantities, may cause adverse symptoms of intoxication. In the USA, the maximum quantity of alcohol included in OTC medicines is 10% v/v for products labeled for use by people of 12 years of age and older, 5% v/v for products intended for use by children aged 6–12 years of age, and 0.5% v/v for products for use by children under 6 years of age.(8)

Parenteral products containing up to 50% of alcohol (ethanol 95 or 96% v/v) have been formulated. However, such concentrations can produce pain on intramuscular injection and lower concentrations such as 5–10% v/v are preferred. Subcutaneous injection of alcohol (ethanol 95% v/v) similarly causes considerable pain followed by anesthesia. If injections are made close to nerves, neuritis and nerve degeneration may occur. This effect is used therapeutically to cause anesthesia in cases of severe pain, although the practice of using alcohol in nerve blocks is controversial. Doses of 1 mL of absolute alcohol have been used for this purpose.(9)

Preparations containing more than 50% v/v alcohol may cause skin irritation when applied topically.

LD_{50} (mouse, IP): 0.93 g/kg(10)
LD_{50} (mouse, IV): 1.97 g/kg
LD_{50} (mouse, oral): 3.45 g/kg
LD_{50} (mouse, SC): 8.29 g/kg
LD_{50} (rat, IP): 3.75 g/kg
LD_{50} (rat, IV): 1.44 g/kg
LD_{50} (rat, oral): 7.06 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Ethanol and aqueous ethanol solutions should be handled in a well-ventilated environment. In the UK, the long-term 8-hour TWA exposure limit for ethanol is 1920 mg/m^3 (1000 ppm).(11) Ethanol may be irritant to the eyes and mucous membranes and eye protection and gloves are recommended. Ethanol is flammable and should be heated with care. Fixed storage tanks should be electrically grounded to avoid ignition from electrostatic discharges when ethanol is transferred.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (dental preparations; inhalations; IM, IV, and SC injections; nasal and ophthalmic preparations; oral capsules, solutions, suspensions, syrups, and tablets; rectal, topical, and transdermal preparations). Included in the Canadian List of Acceptable Non-medicinal Ingredients. Included in nonparenteral and parenteral medicines licensed in the UK.

17 Related Substances

Dehydrated alcohol; denatured alcohol; dilute alcohol; isopropyl alcohol.

Dehydrated alcohol

Synonyms: absolute alcohol; anhydrous ethanol; ethanol.
Autoignition temperature: 365°C
Boiling point: 78.5°C
Explosive limits: 3.5–19.0% v/v in air
Flash point: 12°C (closed cup)
Melting point: −112°C
Moisture content: absorbs water rapidly from the air.

Refractive index: $n_D^{20} = 1.361$
Specific gravity: 0.7904–0.7935 at 20°C
Surface tension: 22.75 mN/m at 20°C (ethanol/vapor)
Vapor density (relative): 1.59 (air = 1)
Vapor pressure: 5.8 Pa at 20°C
Viscosity (dynamic): 1.22 mPa s (1.22 cP) at 20°C
Comments: dehydrated alcohol is ethanol ⩾99.5% v/v. *See* Section 8.

Denatured alcohol

Synonyms: industrial methylated spirit; surgical spirit.
Comments: denatured alcohol is alcohol intended for external use only. It has been rendered unfit for human consumption by the addition of a denaturing agent such as methanol or methyl isobutyl ketone.

Dilute alcohol

Synonyms: dilute ethanol.
Specific gravity: *see* Table III.

Table III: Specific gravity of alcohol.

Strength of alcohol (% v/v)	Specific gravity at 20°C
90	0.8289–0.8319
80	0.8599–0.8621
70	0.8860–0.8883
60	0.9103–0.9114
50	0.9314–0.9326
45	0.9407–0.9417
25	0.9694–0.9703
20	0.9748–0.9759

Comments: the term ‘dilute alcohol’ refers to a mixture of ethanol and water of stated concentration. The BP 2004 lists eight strengths of dilute alcohol (dilute ethanol) containing 90%, 80%, 70%, 60%, 50%, 45%, 25%, and 20% v/v respectively of ethanol.

18 Comments

Possession and use of nondenatured alcohols are usually subject to close control by excise authorities.

A specification for alcohol is contained in the Food Chemicals Codex (FCC).

The EINECS number for alcohol is 200-578-6.

19 Specific References

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21 Authors

SC Owen.

22 Date of Revision

10 February 2005.

Alginic Acid

1 Nonproprietary Names

BP: Alginic acid
PhEur: Acidum alginicum
USPNF: Alginic acid

2 Synonyms

E400; *Kelacid*; L-gulo-D-mannoglycuronan; polymannuronic acid; *Protacid*; *Satialgine H8*.

3 Chemical Name and CAS Registry Number

Alginic acid [9005-32-7]

4 Empirical Formula and Molecular Weight

Alginic acid is a linear glycuronan polymer consisting of a mixture of β-(1→4)-D-mannosyluronic acid and α-(1→4)-L-gulosyluronic acid residues, of general formula $(C_6H_8O)_n$. The molecular weight is typically 20 000–240 000.

5 Structural Formula

The PhEur 2005 describes alginic acid as a mixture of polyuronic acids $[(C_6H_8O_6)_n]$ composed of residues of D-mannuronic and L-glucuronic acid, and is obtained mainly from algae belonging to the Phaeophyceae. A small proportion of the carboxyl groups may be neutralized.

See also Section 4.

6 Functional Category

Stabilizing agent; suspending agent; sustained release adjuvant; tablet binder; tablet disintegrant; viscosity-increasing agent.

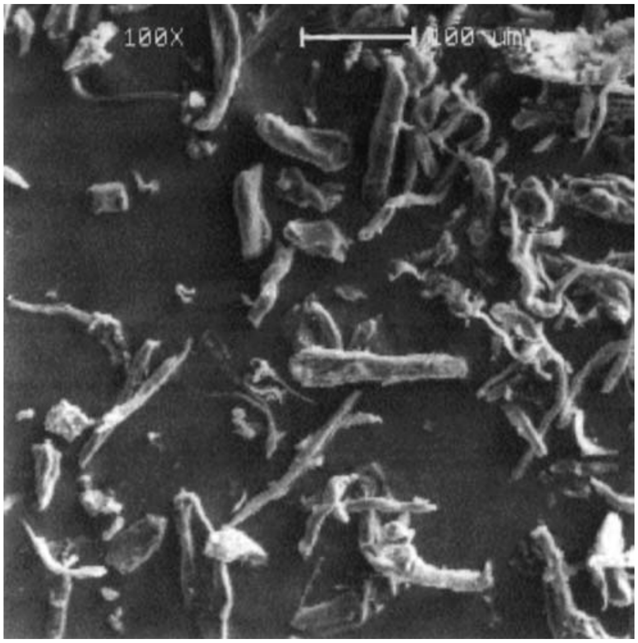
7 Applications in Pharmaceutical Formulation or Technology

Alginic acid is used in a variety of oral and topical pharmaceutical formulations. In tablet and capsule formulations, alginic acid is used as both a binder and disintegrating agent at concentrations of 1–5% w/w.(1,2) Alginic acid is widely used as a thickening and suspending agent in a variety of pastes, creams, and gels; and as a stabilizing agent for oil-in-water emulsions. Alginic acid has also been investigated for use in an ocular formulation of carteolol.(3)

Therapeutically, alginic acid has been used as an antacid.(4) In combination with an H_2-receptor antagonist, it has also been utilized for the management of gastroesophageal reflux.(5) Chemically modified alginic acid derivatives have been researched for their anti-inflammatory, antiviral, and antitumoral activities.(6)

In the area of controlled release, the preparation of indomethacin sustained-release microparticles from alginic acid (alginate)–gelatin hydrocolloid coacervate systems has been investigated.(7) In addition, as controlled-release systems for liposome-associated macromolecules, microspheres have been produced encapsulating liposomes coated with alginic acid and poly-L-lysine membranes.(8) Alginate gel beads capable of floating in the gastric cavity have been prepared, the release properties of which were reported to be applicable for sustained release of drugs, and for tareting the gastric mucosa.(9) Alginic acid has also been used to improve the stability of levosimendan.(10) Mechanical properties, water uptake, and permeability properties of a sodium salt of alginic acid have been characterized for controlled-release applications.(11) In addition, sodium alginate has been incorporated into an ophthalmic drug delivery system for pilocarpine nitrate.(12) It has also been reported that associated chains of alginic acid complexed with cations can bind to cell surfaces and exert pharmacological effects which depend on the cell type and the complexed cation. These complexes can be used to treat rheumatic disorders, diseases associated with atopic diathesis and liver diseases.(13) Furthermore, an alginic oligosaccharide, obtained from a natural edible polysaccharide, has been shown to suppress Th2 responses and IgE production by inducing IL-12 production, was found to be a useful approach for preventing allergic disorders.(14)

SEM: 1
Excipient: Alginic acid
Magnification: 100×
Voltage: 25 kV



8 Description

Alginic acid is a tasteless, practically odorless, white to yellowish-white, fibrous powder.

9 Pharmacopeial Specifications

See Table I.

SEM: 2
Excipient: Alginic acid
Magnification: 500×
Voltage: 25 kV

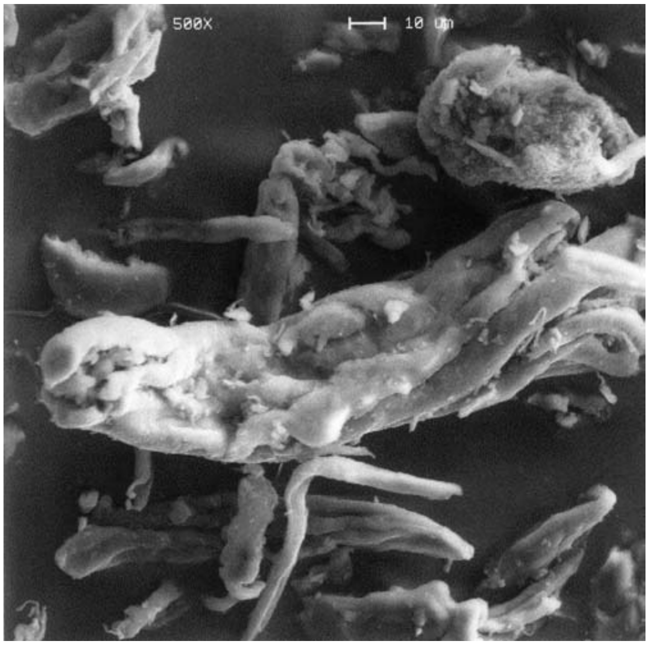


Table I: Pharmacopeial specifications for alginic acid

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Microbial limits	⩽10^2/g	⩽200/g
pH (3% dispersion)	—	1.5–3.5
Loss on drying	⩽15.0%	⩽15.0%
Ash	—	⩽4.0%
Sulfated ash	⩽8.0%	—
Arsenic	—	⩽3 ppm
Chloride	⩽1.0%	—
Lead	—	⩽0.001%
Heavy metals	⩽20 ppm	⩽0.004%
Acid value (dried basis)	—	⩾230
Assay (of COOH groups)	19.0–25.0%	—

10 Typical Properties

Acidity/alkalinity: pH = 1.5–3.5 for a 3% w/v aqueous dispersion.

Crosslinking: addition of a calcium salt, such as calcium citrate or calcium chloride, causes crosslinking of the alginic acid polymer resulting in an apparent increase in molecular weight. Films crosslinked with triphosphate (tripolyphosphate) and calcium chloride were found to be insoluble but permeable to water vapor. Drug permeability varies with pH and the extent of crosslinking.(11)

Density (true): 1.601 g/cm^3

Moisture content: 7.01%

Solubility: soluble in alkali hydroxides, producing viscous solutions; very slightly soluble or practically insoluble in ethanol (95%) and other organic solvents. Alginic acid swells in water but does not dissolve; it is capable of absorbing 200–300 times its own weight of water.

Viscosity (dynamic): various grades of alginic acid are commercially available that vary in their molecular weight and hence viscosity. Viscosity increases considerably with increasing concentration; typically a 0.5% w/w aqueous dispersion will have a viscosity of approximately 20 mPa s, while a 2.0% w/w aqueous dispersion will have a viscosity of approximately 2000 mPa s. The viscosity of dispersions decreases with increasing temperature. As a general rule, a 1°C increase in temperature results in a 2.5% reduction in viscosity. At low concentrations, the viscosity of an alginic acid dispersion may be increased by the addition of a calcium salt, such as calcium citrate. *See also* Sections 11 and 18.

11 Stability and Storage Conditions

Alginic acid hydrolyzes slowly at warm temperatures producing a material with a lower molecular weight and lower dispersion viscosity.

Alginic acid dispersions are susceptible to microbial spoilage on storage, which may result in some depolymerization and hence a decrease in viscosity. Dispersions should therefore be preserved with an antimicrobial preservative such as benzoic acid; potassium sorbate; sodium benzoate; sorbic acid; or paraben. Concentrations of 0.1–0.2% are usually used.

Alginic acid dispersions may be sterilized by autoclaving or filtration through a 0.22 μm filter. Autoclaving may result in a decrease in viscosity which can vary depending upon the nature of any other substances present.(15)

Alginic acid should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatible with strong oxidizing agents, alginic acid forms insoluble salts in the presence of alkaline earth metals and group III metals with the exception of magnesium.

13 Method of Manufacture

Alginic acid is a hydrophilic colloid carbohydrate that occurs naturally in the cell walls and intercellular spaces of various species of brown seaweed (Phaeophyceae). The seaweed occurs widely throughout the world and is harvested, crushed, and treated with dilute alkali to extract the alginic acid.

14 Safety

Alginic acid is widely used in food products and topical and oral pharmaceutical formulations. It is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may be harmful. Inhalation of alginate dust may be irritant and has been associated with industrially related asthma in workers involved in alginate production. However, it appears that the cases of asthma were linked to exposure to unprocessed seaweed dust rather than pure alginate dust.(16) An acceptable daily intake of alginic acid and its ammonium, calcium, potassium, and sodium salts was not set by the WHO because the quantities used, and the background levels in food, did not represent a hazard to health.(17)

LD_{50} (rat, IP): 1.6 g/kg(18)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Alginic acid may be irritant to the eyes or respiratory system if inhaled as dust; *see* Section 14. Eye protection, gloves, and a dust respirator are recommended. Alginic acid should be handled in a well-ventilated environment.

16 Regulatory Status

GRAS listed. Accepted in Europe for use as a food additive. Included in the FDA Inactive Ingredients Guide (ophthalmic preparations, oral capsules, and tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients. Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Ammonium alginate; calcium alginate; potassium alginate; propylene glycol alginate; sodium alginate.

18 Comments

Alginic acid dispersions are best prepared by pouring the alginic acid slowly and steadily into vigorously stirred water. Dispersions should be stirred for approximately 30 minutes. Premixing the alginic acid with another powder, such as sugar, or a water-miscible liquid such as ethanol (95%) or glycerin, aids dispersion.

When using alginic acid in tablet formulations, the alginic acid is best incorporated or blended using a dry granulation process.

A specification for alginic acid is contained in the Food Chemicals Codex (FCC).

The EINECS number for alginic acid is 232-680-1.

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21 Authors

JW McGinity, MA Repka.

22 Date of Revision

23 August 2005.

Aliphatic Polyesters

1 Nonproprietary Names

See Table I.

2 Synonyms

See Table I.

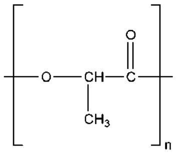
3 Chemical Name and CAS Registry Number

See Table I.

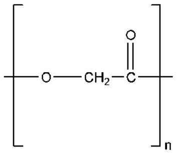
4 Empirical Formula and Molecular Weight

Aliphatic polyesters are synthetic homopolymers or copolymers of lactic acid, glycolic acid, and ε-hydroxycaproic acid. Typically, the molecular weights of homopolymers and copolymers range from 2000 to >100 000.

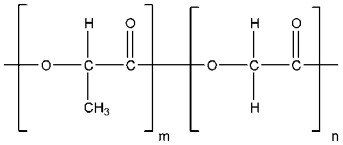
5 Structural Formula



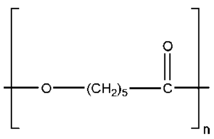
Poly(lactide)



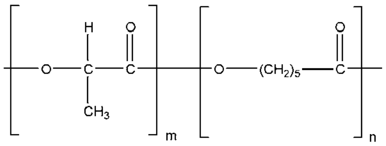
Poly(glycolide)



Poly(lactide-co-glycolide)



Polycaprolactone



Poly(lactide-co-caprolactone)

6 Functional Category

Bioabsorbable; biocompatible; biodegradable material.

7 Applications in Pharmaceutical Formulation or Technology

Aliphatic polyesters are a group of synthesized, nontoxic, biodegradable polymers. In an aqueous environment, they undergo hydrolytic degradation, through cleavage of the ester linkages, into nontoxic hydroxycarboxylic acids. Aliphatic polyesters are eventually metabolized to carbon dioxide and water, via the citric acid cycle. Owing to their reputation as safe materials and their biodegradability, aliphatic polyesters are primarily used as biocompatible and biodegradable polymers for formulation of many types of implantable and injectable drug-delivery systems for both human and veterinary use. Examples of implantable drug delivery systems include rods, cylinders, tubing, films,(1) fibers,(2) pellets, and beads.(3) Examples of injectable drug-delivery systems include microcapsules,(4) microspheres,(5) nanoparticles, and liquid injectable controlled-release systems. The rate of biodegradation and drug-release characteristics from these systems formulated with the aliphatic polyesters can be controlled by changing the physicochemical properties of the polymers, such as crystallinity, hydrophobicity, monomer stereochemistry, copolymer ratio, and polymer molecular weight.

8 Description

Aliphatic polyesters are a group of synthesized homopolymers or copolymers. They are nontoxic and can easily be fabricated into a variety of novel devices, such as rods, screws, nails, and cylinders. The polymers are commercially available in varying molecular weights as both homopolymers and copolymers. Molecular weights of polyesters range from 2000 to greater than 100 000.

Co-monomer ratios of lactic acid and glycolic acid for poly(DL-lactide-co-glycolide) range from 85 : 15 to 50 : 50. Table I shows the chemical and trade names of different commercially available aliphatic polyesters.

9 Pharmacopeial Specifications

—

10 Typical Properties

For typical physical and mechanical properties of the aliphatic polyesters, *see* Table II.

Polymer composition and crystallinity play important roles in the solubility of these aliphatic polyesters. The crystalline homopolymers of glycolic acid are soluble only in strong solvents, such as hexafluoroisopropanol. The crystalline homopolymers of lactic acid also do not have good solubility in most organic solvents. However, amorphous polymers of DL-lactic acid and copolymers of lactic acid and glycolic acid with a low glycolic acid content are soluble in many organic solvents (Table II). Aliphatic polyesters are slightly soluble or insoluble in water, methanol, ethylene glycol, heptane, and hexane.

Table I: Chemical names and CAS registry numbers of the aliphatic polyesters.

Generic name	Composition (%)			Synonyms	Trade name	Manufacturer	CAS name	CAS number
	Lactide	Glycolide	Caprolactone					
Poly(D-lactide)	100	0	0	D-PLA	*Purasorb PD*	PURAC	(3*R*-cis)-3,6-Dimethyl-1,4-dioxane-2,5-dione homopolymer	[25038-75-9]
Poly(L-lactide)	100	0	0	L-PLA	*Lactel* L-PLA	BPI	Propanoic acid, 2-hydroxy-, homopolymer	[26161-42-2]
					Medisorb 100 L	Alkermes		
					Purasorb PL	PURAC		
					Resomer L 206, 207, 209, 210, 214	BI		
Poly(DL-lactide)	100	0	0	DL-PLA	*Lactel* DL-PLA	BPI	Propanoic acid, 2-hydroxy-, homopolymer	[34346-01-5]
					Medisorb 100 DL	Alkermes		
					Pursasorb PDL	PURAC		
					Resomer R 202, 202H, 203, 206, 207, 208	BI		
Poly(glycolide)	0	100	0	PGA	*Lactel PGA*	BPI	Acetic acid, hydroxy-, homopolymer	[34346-01-5]
					Medisorb 100 PGA	Alkermes		
					Purasorb PG	PURAC		
					Resomer G 205	BI		
Poly(L-lactide-co-glycolide)	75	25	0	L-PLGA (75 : 25)	*Pursasorb* PLG	PURAC	1,4-Dioxane-2,5-dione, polymer with (3*S*-cis)-3,6-dimethyl-1,4-dioxane-2,5-dione	[30846-39-0]
Poly(L-lactide-co-glycolide)	50	50	0	L-PLGA (50 : 50)	*Purasorb PLG*	PURAC	1,4-Dioxane-2,5-dione,polymer with (3*S*-cis)-3,6-dimethyl-1,4-dioxane-2,5-dione	[30846-39-0]
Poly(DL-lactide-co-glycolide)	85	15	0	Polyglactin;DL-PLGA (85:15)	*Lactel 8515* DL-PLGA	BPI	Propanoic acid, 2-hydroxypolymer with hydroxyacetic acid	[26780-50-7]
					Medisorb 8515 DL	Alkermes		
					Resomer RG 858	BI		
Poly(DL-lactide-co-glycolide)	75	25	0	Polyglactin;DL-PLGA (75 : 25)	*Lactel 7525* DL-PLGA	BPI	Propanoic acid, 2-hydroxypolymer with hydroxyacetic acid	[26780-50-7]
					Pursasorb PDLG	PURAC		
					Resomer RG 752, 755, 756	BI		
Poly(DL-lactide-co-glycolide)	65	35	0	Polyglactin;DL-PLGA (65 : 35)	*Lactel 6535* DL-PLGA	BPI	Propanoic acid, 2-hydroxypolymer with hydroxyacetic acid	[26780-50-7]
Poly(DL-lactide-co-glycolide)	50	50	0	Polyglactin;DL-PLGA (50 : 50)	*Lactel 5050* DL-PLGA	BPI	Propanoic acid, 2-hydroxypolymer with hydroxyacetic acid	[26780-50-7]
					Medisorb 5050 DL	Alkermes		
					Purasorb PDLG	PURAC		
					Resomer RG 502, 502H, 503, 503H, 504, 504H, 505, 506	BI		
Poly-ε-caprolactone	0	0	100	PCL	*Lactel PCL*	BPI	2-Oxepanone, homopolymer	[24980-41-4]
Poly(DL-lactide-co-caprolactone)	75	0	25	DL-PLCL (75 : 25)	*Lactel 7525* DL-PLCL	BPI	1,4-Dioxane-2,5-dione,3,6-dimethyl-, polymer with 2-oxepanone	[70524-20-8]
Poly(DL-lactide-co-caprolactone)	25	0	75	DL-PLCL (25 : 75)	*Lactel 2575* DL-PLCL	BPI	1,4-Dioxane-2,5-dione,3,6-dimethyl-, polymer with 2-oxepanone	[70524-20-8]

Alkermes, Alkermes Inc.; BI, Boehringer Ingelheim; BPI, Birmingham Polymers Inc.; PURAC, PURAC America.

Table II: Typical physical and mechanical properties of the aliphatic polyesters.[a]

	50/50 DL-PLG	**65/35 DL-PLG**	**75/25 DL-PLG**	**85/15 DL-PLG**	**DL-PLA**	**L-PLA**	**PGA**	**PCL**
Molecular weight	40 000–100 000	40 000–100 000	40 000–100 000	40 000–100 000	40 000–100 000	>100 000	>100 000	80–150 000
Inherent viscosity (mPa s)	0.5–0.8[b]	0.5–0.8[b]	0.5–0.8[c]	0.5–0.8[c]	0.5–0.8[c]	0.9–1.2[c]	1.1–1.4[b]	0.7–1.3[c]
Melting point (°C)	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous	173–178	225–230	58–63
Glass transition (°C)	45–50	45–50	50–55	50–55	55–60	60–65	35–40	–65 to –60
Color	White to light gold	White to light gold	White to light gold	White to light gold	White	White	Light tan	White
Solubility[d]	$MeCl_2$, THF, EtOAc, C_3H_6O, $CHCl_3$	$MeCl_2$, THF, EtOAc, C_3H_6O, $CHCl_3$	$MeCl_2$, THF, EtOAc, C_3H_6O, $CHCl_3$	$MeCl_2$, THF, EtOAc, C_3H_6O, $CHCl_3$,	$MeCl_2$, THF, EtOAc, C_3H_6O, $CHCl_3$	$MeCl_2$, $CHCl_3$	HFIP, HFASH	$MeCl_2$, $CHCl_3$, C_3H_6O
Specific gravity	1.34	1.30	1.30	1.27	1.25	1.24	1.53	1.11
Tensile strength (psi)	6000–8000	6000–8000	6000–8000	6000–8000	4000–6000	8000–12 000	10 000+	3000–5000
Elongation (%)	3–10	3–10	3–10	3–10	3–10	5–10	15–20	300–500
Modulus (psi)	$2–4 \times 10^5$	$2–4 \times 10^5$	$2–4 \times 10^5$	$2–4 \times 10^5$	$2–4 \times 10^5$	$4–6 \times 10^5$	1×10^6	$3–5 \times 10^4$

Note: DL-PLG: DL-poly(lactic-co-glycolic acid); DL-PLA: DL-polylactic acid; L-PLA: L-polylactic acid; PGA: polyglycolic acid; PCL: poly-ε-caprolactone.

[a] Specifications obtained from Birmingham Polymers, Inc.

[b] (HFIP) hexafluoroisopropanol.

[c] ($CHCl_3$) chloroform.

[d] Partial listing only: $MeCl_2$, methylene chloride; THF, tetrahydrofuran; EtOAc, ethyl acetate; HFIP, hexafluoroisopropanol; HFASH, hexafluoroacetone sesquihydrate; C_3H_6O, acetone.

11 Stability and Storage Conditions

The aliphatic polyesters are easily susceptible to hydrolysis in the presence of moisture. Hence, they should be properly stored, preferably refrigerated at below 0°C. It is necessary to allow the polymers to reach room temperature before opening the container. After the original package has been opened, it is recommended to re-purge the package with high-purity dry nitrogen prior to resealing.

12 Incompatibilities

—

13 Method of Manufacture

Generally, aliphatic polyesters can be synthesized via polycondensation of hydroxycarboxylic acids and catalytic ring-opening polymerization of lactones. Ring-opening polymerization is preferred because polyesters with high molecular weights can be produced. Moreover, the dehydration of hydroxycarboxylic acids to form lactones does not have to be carried to a high degree of completion. Lactones can easily be purified owing to the differences of their physical and chemical properties from those of the corresponding hydroxycarboxylic acid.

14 Safety

Poly(lactide), poly(glycolide), poly(lactide-co-glycolide), and polycaprolactone are used in parenteral pharmaceutical formulations and are regarded as biodegradable, biocompatible, and bioabsorbable materials. Their biodegradation products are nontoxic, noncarcinogenic, and nonteratogenic. In general, these polyesters exhibit very little hazard.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Contact with eyes, skin, and clothing, and breathing the dust of the polymers should be avoided. Aliphatic polyesters produce acid materials such as hydroxyacetic and/or lactic acid in the presence of moisture; thus, contact with materials that will react with acids, especially in moist conditions, should be avoided.

16 Regulatory Status

GRAS listed. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Lactic acid.

18 Comments

Due to their ability to form complexes with heavy metal ions, aliphatic polyesters are added to skin-protective ointments.(6)

19 Specific References

1 Jackanicz TM, Nash HA, Wise DL, Gregory JB. Polylactic acid as a biodegradable carrier for contraceptive steroids. *Contraception* 1973; **8**: 227–233.

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21 Authors

RK Chang, AJ Shukla, Y Sun.

22 Date of Revision

26 August 2005.

Alitame

1 Nonproprietary Names

None adopted.

2 Synonyms

Aclame; L-aspartyl-D-alanine-*N*-(2,2,4,4-tetramethylthietan-3-yl)amide; 3-(L-aspartyl-D-alaninamido)-2,2,4,4-tetramethylthietane.

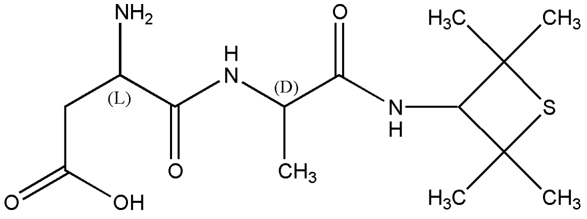
3 Chemical Name and CAS Registry Number

L-α-Aspartyl-*N*-(2,2,4,4-tetramethyl-3-thietanyl)-D-alaninamide anhydrous [80863-62-3]
L-α-Aspartyl-*N*-(2,2,4,4-tetramethyl-3-thietanyl)-D-alaninamide hydrate [99016-42-9]

4 Empirical Formula and Molecular Weight

$C_{14}H_{25}N_3O_4S$	331.44 (for anhydrous)
$C_{14}H_{25}N_3O_4S{\cdot}2\frac{1}{2}H_2O$	376.50 (for hydrate)

5 Structural Formula



6 Functional Category

Sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

Alitame is an intense sweetening agent developed in the early 1980s and is approximately 2000 times sweeter than sucrose. It has an insignificant energy contribution of 6 kJ (1.4 kcal) per gram of alitame.

Alitame is currently primarily used in a wide range of foods and beverages at a maximum level of 40–300 mg/kg.(1)

8 Description

Alitame is a white nonhygroscopic crystalline powder; odorless or having a slight characteristic odor.

9 Pharmacopeial Specifications

—

10 Typical Properties

Acidity/alkalinity: pH = 5–6 (5% w/v aqueous solution)

Isoelectric point: pH 5.6

Melting point: 136–147°C

Solubility: *see* Table I.

Table I: Solubility of alitame.

Solvent	Solubility at 20°C unless otherwise stated
Chloroform	1 in 5000 at 25°C
Ethanol	1 in 1.6 at 25°C
n-Heptane	Practically insoluble
Methanol	1 in 2.4 at 25°C
Propylene glycol	1 in 1.9 at 25°C
Water	1 in 8.3 at 5°C
	1 in 7.6 at 25°C
	1 in 3.3 at 40°C
	1 in 2.0 at 50°C

Specific rotation $[\alpha]_D^{25}$: +40° to +50° (1% w/v aqueous solution)

11 Stability and Storage Conditions

Alitame is stable in dry, room temperature conditions but undergoes degradation at elevated temperatures or when in solution at low pH. Alitame can degrade in a one-stage process to aspartic acid and alanine amide (under harsh conditions) or in a slow two-stage process by first degrading to its β-aspartic isomer and then to aspartic acid and alanine amide. At pH 5–8, alitame solutions at 23°C have a half-life of approximately 4 years. At pH 2 and 23°C the half-life is 1 year.

Alitame should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Alitame may be incompatible with oxidizing and reducing substances or strong acids and bases.

13 Method of Manufacture

Alitame may be synthesized by a number of routes.(2,3) For example, 3-(D-alaninamido)-2,2,4,4-tetramethylthietane is dissolved in water and L-aspartic acid *N*-thiocarboxyanhydride is then added in portions with vigorous stirring, maintaining the pH of 8.5–9.5. The pH is then adjusted to 5.5 and *p*-toluenesulfonic acid monohydrate is added over a period of one hour. The precipitated crystalline *p*-toluenesulfonate salt is collected by filtration. To obtain alitame from its salt, a mixture of *Amberlite LA-1* (liquid anion exchange resin), dichloromethane, deionized water, and the salt is stirred for one hour, resulting in two clear layers. The aqueous layer is treated with carbon, clarified by filtration, and cooled to crystallize alitame.

Alternatively, tetramethylthietane amine is condensed with an *N*-protected form of D-alanine to give alanyl amide. This is then coupled to a protected analogue of L-aspartic acid to give a crude form of alitame. The crude product is then purified.

14 Safety

Alitame is a relatively new intense sweetening agent used primarily in foods and confectionary. It is generally regarded as a relatively nontoxic and nonirritant material.

Chronic animal studies in mice, rats, and dogs carried out for a minimum of 18 months at concentrations >100 mg/kg per day exhibited no toxic or carcinogenic effects. In people, no evidence of untoward effects were observed following ingestion of 15 mg/kg per day for two weeks.

Following oral administration 7–22% of alitame is unabsorbed and excreted in the feces. The remaining amount is hydrolyzed to aspartic acid and alanine amide. The aspartic acid is metabolized normally and the alanine amide excreted in the urine as a sulfoxide isomer, as the sulfone, or conjugated with glucuronic acid.

The WHO has set an acceptable daily intake of alitame at up to 0.1 mg/kg body-weight.(4)

LD_{50} (mouse, oral): >5 g/kg
LD_{50} (rabbit, skin): >2 g/kg
LD_{50} (rat, oral): >5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Alitame should be stored in tightly closed containers, and protected from exposure to direct sunlight and higher than normal room temperatures.

16 Regulatory Status

Alitame is approved for use in food applications in a number of countries worldwide including Australia, Chile, China, Mexico, and New Zealand.

17 Related Substances

Acesulfame potassium; aspartame; saccharin; saccharin sodium; sodium cyclamate.

18 Comments

—

19 Specific References

1 FAO/WHO. Evaluation of certain food additives and contaminants. Fifty-ninth report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 2002; No. 913.
2 Sklavounos C. Process for preparation, isolation and purification of dipeptide sweeteners. United States Patent No. 4,375,430; 1 Mar, 1983.
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21 Authors

LY Galichet.

22 Date of Revision

17 August 2005.

Almond Oil

1 Nonproprietary Names

BP: Almond oil
PhEur: Amygdalae oleum virginum
USPNF: Almond oil

2 Synonyms

Almond oil, bitter; artificial almond oil; bitter almond oil; expressed almond oil; huile d'amande; oleo de amêndoas; olio di mandorla; sweet almond oil; virgin almond oil.

3 Chemical Name and CAS Registry Number

Almond oil [8007-69-0]

4 Empirical Formula and Molecular Weight

Almond oil consists chiefly of glycerides of oleic acid, with smaller amounts of linoleic and palmitic acids. The PhEur 2005 describes almond oil as the fatty oil obtained by cold expression from the ripe seeds of *Prunus dulcis* (Miller) DA Webb var. *dulcis* or *Prunus dulcis* (Miller) DA Webb var. *amara* (DC) Buchheim or a mixture of both varieties. A suitable antioxidant may be added.

The USPNF 23 describes almond oil as the fixed oil obtained by expression from the kernels of varieties of *Prunus amygdalus* Batsch (Fam. Rosaceae).

5 Structural Formula

See above.

6 Functional Category

Emollient; oleaginous vehicle; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Almond oil is used therapeutically as an emollient(1) and to soften ear wax. As a pharmaceutical excipient it is employed as a vehicle in parenteral preparations,(2) such as oily phenol injection. It is also used in nasal spray,(3) and topical preparations.(4) Almond oil is also consumed as a food substance, *see* Section 18.

8 Description

A clear, colorless, or pale-yellow colored oil with a bland, nutty taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for almond oil.

Test	PhEur 2005	USPNF 23
Identification	+	+
Absorbance	+	—
Acid value	⩽2.0	—
Characters	+	—
Cottonseed oil	—	+
Foreign kernel oils	—	+
Foreign oils	—	+
Iodine value	—	95–105
Mineral oil and fatty oils	—	+
Peroxide value	⩽15.0	—
Saponification value	—	190–200
Sesame oil	—	+
Specific gravity	—	0.910–0.915
Unsaponifiable matter	⩽0.7%	—
Free fatty acids	+	+
Saturated fatty acids $< C_{16}$	⩽0.1%	—
Arachidic acid	⩽0.2%	—
Behenic acid	⩽0.2%	—
Eicosenoic acid	⩽0.3%	—
Erucic acid	⩽0.1%	—
Linoleic acid	20.0–30.0%	—
Linolenic acid	⩽0.4%	—
Margaric acid	⩽0.2%	—
Oleic acid	62.0–86.0%	—
Palmitic acid	4.0–9.0%	—
Palmitoleic acid	⩽0.6%	—
Stearic acid	⩽3.0%	—
Sterols	+	—
Δ^5-Avenasterol	⩾10.0%	—
Δ^7-Avenasterol	⩽3.0%	—
Brassicasterol	⩽0.3%	—
Cholesterol	⩽0.7%	—
Campesterol	⩽4.0%	—
Stigmasterol	⩽3.0%	—
β-Sitosterol	73.0–87.0%	—
Δ^7-Stigmasterol	⩽3.0%	—

10 Typical Properties

Flash point: 320°C
Melting point: −18°C
Refractive index: $n_{D}^{40} = 1.4630–1.4650$
Smoke point: 220°C
Solubility: miscible with chloroform, and ether; slightly soluble in ethanol (95%).

11 Stability and Storage Conditions

Almond oil should be stored in a well-closed container in a cool, dry place away from direct sunlight and odors. It may be sterilized by heating at 150°C for 1 hour. Almond oil does not easily turn rancid.

12 Incompatibilities

—

13 Method of Manufacture

Almond oil is expressed from the seeds of the bitter or sweet almond, *Prunus dulcis (Prunus amygdalus; Amygdalus communis)* var. *amara* or var. *dulcis* (Rosaceae).(5) *See also* Section 4.

14 Safety

Almond oil is widely consumed as a food and is used both therapeutically and as an excipient in topical and parenteral pharmaceutical formulations, where it is generally regarded as a nontoxic and nonirritant material. However, there has been a single case reported of a 5-month-old child developing allergic dermatitis attributed to the application of almond oil for 2 months to the cheeks and buttocks.(6)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Included in nonparenteral and parenteral medicines licensed in the UK. Widely used as an edible oil.

17 Related Substances

Canola oil; corn oil; cottonseed oil; peanut oil; refined almond oil; sesame oil; soybean oil.

Refined almond oil

Synonyms: amygdalae oleum raffinatum.

Comments: refined almond oil is defined in some pharmacopeias such as the PhEur 2005. Refined almond oil is a clear, pale yellow colored oil with virtually no taste or odor. It is obtained by expression of almond seeds followed by subsequent refining. It may contain a suitable antioxidant.

18 Comments

A 100 g quantity of almond oil has a nutritional energy value of 3700 kJ (900 kcal) and contains 100 g of fat of which 28% is polyunsaturated, 64% is monounsaturated and 8% is saturated fat.

Studies have suggested that almond consumption is associated with health benefits, including a decreased risk of colon cancer.(7)

A specification for bitter almond oil is contained in the Food Chemicals Codex (FCC).

19 Specific References

1 Pesko LJ. Peanut recipe softens brittle, split nails. *Am Drug* 1997; **214**(Dec): 48.

2 Van Hoogmoed LM, Agnew DW, Whitcomb M, *et al*. Ultrasonographic and histologic evaluation of medial and middle patellar ligaments in exercised horses following injection with ethanolamine oleate and 2% iodine in almond oil. *Am J Vet Res* 2002; **63**(5): 738–743.

3 Cicinelli E, Savino F, Cagnazzo I, *et al*. Progesterone administration by nasal spray in menopausal women: comparison between two different spray formulations. *Gynecol Endocrinol* 1992; **6**(4): 247–251.

4 Christen P, Kloeti F, Gander B. Stability of prednisolone and prednisolone acetate in various vehicles used in semi-solid topical preparations. *J Clin Pharm Ther* 1990; **15**(5): 325–329.

5 Evans WC. *Trease and Evans' Pharmacognosy*, 14th edn. London: WB Saunders, 1996: 184.

6 Guillet G, Guillet M-H. Percutaneous sensitization to almond in infancy and study of ointments in 27 children with food allergy. *Allerg Immunol* 2000; **32**(8): 309–311.

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21 Authors

SA Shah, D Thassu.

22 Date of Revision

15 August 2005.

Alpha Tocopherol

1 Nonproprietary Names

BP: Alpha tocopherol
JP: Tocopherol
PhEur: RRR-α-Tocopherolum
USP: Vitamin E
See also Sections 3, 9, and 17.

2 Synonyms

Copherol F1300; (±)-3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-6-ol; E307; *Eastman Vitamin E TPGS*; synthetic alpha tocopherol; all-*rac*-α-tocopherol; *dl*-α-tocopherol; 5,7,8-trimethyltocol.

3 Chemical Name and CAS Registry Number

(±)-(2RS,4′RS,8′RS)-2,5,7,8-Tetramethyl-2-(4′,8′,12′-trimethyltridecyl)-6-chromanol [10191-41-0]

Note that alpha tocopherol has three chiral centers, giving rise to eight isomeric forms. The naturally occurring form is known as *d*-alpha tocopherol or (2*R*,4′*R*,8′*R*)-alpha-tocopherol. The synthetic form, *dl*-alpha tocopherol or simply alpha tocopherol, occurs as a racemic mixture containing equimolar quantities of all the isomers.

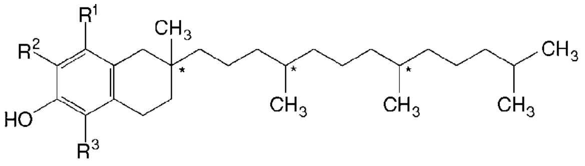
Similar considerations apply to beta, delta, and gamma tocopherol and tocopherol esters.

See Section 17 for further information.

4 Empirical Formula and Molecular Weight

$C_{29}H_{50}O_2$ 430.72

5 Structural Formula



Alpha tocopherol: $R^1 = R^2 = R^3 = CH_3$
Beta tocopherol: $R^1 = R^3 = CH_3$; $R^2 = H$
Delta tocopherol: $R^1 = CH_3$; $R^2 = R^3 = H$
Gamma tocopherol: $R^1 = R^2 = CH_3$; $R^3 = H$
* Indicates chiral centers.

6 Functional Category

Antioxidant; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Alpha tocopherol is primarily recognized as a source of vitamin E, and the commercially available materials and specifications reflect this purpose. While alpha tocopherol also exhibits antioxidant properties, the beta, delta, and gamma tocopherols are considered to be more effective as antioxidants.

Alpha-tocopherol is a highly lipophilic compound, and is an excellent solvent for many poorly soluble drugs.(1–4) Of widespread regulatory acceptability, tocopherols are of value in oil- or fat-based pharmaceutical products and are normally used in the concentration range 0.001–0.05% v/v. There is frequently an optimum concentration; thus the autoxidation of linoleic acid and methyl linolenate is reduced at low concentrations of alpha tocopherol, and is accelerated by higher concentrations. Antioxidant effectiveness can be increased by the addition of oil-soluble synergists such as lecithin and ascorbyl palmitate.(4)

D-α-Tocopherol has also been used as a non-ionic surfactant in oral and injectable formulations.(3)

8 Description

Alpha tocopherol is a natural product. The PhEur 2005 (Suppl. 5.1) describes α-tocopherol as a clear, colorless or yellowish-brown, viscous, oily liquid. *See also* Section 17.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for alpha tocopherol.

Test	JP 2001	PhEur 2005 (Suppl. 5.1)	USP 28
Identification	+	+	+
Characters	—	+	—
Acidity	—	—	+
Acid value	—	⩽2	—
Optical rotation	—	–0.01° to +0.01°	+
Heavy metals	⩽20 ppm	⩽20 ppm	—
Sulfated ash	—	⩽0.1%	—
Organic volatile impurities	—	—	+
Absorbance	+	+	—
at 255 nm	—	5.5–8.0	—
at 292 nm	71.0–76.0	72.0–76.0	—
Refractive index	1.503–1.507	—	—
Specific gravity	0.947–0.955	—	—
Clarity and color of solution	+	—	—
Assay	96.0–102.0%	96.0–101.5%	96.0–102.0%

Note that the USP 28 describes vitamin E as comprising *d*- or *dl*-alpha tocopherol, *d*- or *dl*-alpha tocopheryl acetate, or *d*- or *dl*-alpha tocopheryl acid succinate. However, the PhEur 2005 describes alpha tocopherol and alpha tocopheryl acetate in separate monographs.

The diversity of the tocopherols described in the various pharmacopeial monographs makes the comparison of specifications more complicated; *see* Section 17.

10 Typical Properties

Boiling point: 235°C
Density: 0.947–0.951 g/cm^3
Flash point: 240°C
Ignition point: 340°C
Refractive index: n_D^{20} = 1.503–1.507
Solubility: practically insoluble in water; freely soluble in acetone, ethanol, ether, and vegetable oils.

11 Stability and Storage Conditions

Tocopherols are oxidized slowly by atmospheric oxygen and rapidly by ferric and silver salts. Oxidation products include tocopheroxide, tocopherylquinone, and tocopherylhydroquinone, as well as dimers and trimers. Tocopherol esters are more stable to oxidation than the free tocopherols but are in consequence less effective antioxidants. *See also* Section 17.

Tocopherols should be stored under an inert gas, in an airtight container in a cool, dry place and protected from light.

12 Incompatibilities

Tocopherols are incompatible with peroxides and metal ions, especially iron, copper, and silver. Tocopherols may be absorbed into plastic.(5)

13 Method of Manufacture

Naturally occurring tocopherols are obtained by the extraction or molecular distillation of steam distillates of vegetable oils; for example, alpha tocopherol occurs in concentrations of 0.1–0.3% in corn, rapeseed, soybean, sunflower, and wheat germ oils.(6) Beta and gamma tocopherol are usually found in natural sources along with alpha tocopherol. Racemic synthetic tocopherols may be prepared by the condensation of the appropriate methylated hydroquinone with racemic isophytol.(7)

14 Safety

Tocopherols (vitamin E) occur in many food substances that are consumed as part of the normal diet. The daily nutritional requirement has not been clearly defined but is estimated to be 3.0–20.0 mg. Absorption from the gastrointestinal tract is dependent upon normal pancreatic function and the presence of bile. Tocopherols are widely distributed throughout the body, with some ingested tocopherol metabolized in the liver; excretion of metabolites is via the urine or bile. Individuals with vitamin E deficiency are usually treated by oral administration of tocopherols, although intramuscular and intravenous administration may sometimes be used.

Tocopherols are well tolerated, although excessive oral intake may cause headache, fatigue, weakness, digestive disturbance, and nausea. Prolonged and intensive skin contact may lead to erythema and contact dermatitis.

The use of tocopherols as antioxidants in pharmaceuticals and food products is unlikely to pose any hazard to human health since the daily intake from such uses is small compared to the intake of naturally occurring tocopherols in the diet.

The WHO has set an acceptable daily intake of tocopherol used as an antioxidant at 0.15–2.0 mg/kg body-weight.(8)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Gloves and eye protection are recommended.

16 Regulatory Status

GRAS listed. Accepted in Europe as a food additive. Included in the FDA Inactive Ingredients Guide (IV injections, powder, lyophilized powder for liposomal suspension; oral capsules, tablets, and topical preparations). Included in the Canadian List of Acceptable Non-medicinal Ingredients. Included in nonparenteral medicines licensed in the UK.

17 Related Substances

d-Alpha tocopherol; *d*-Alpha tocopheryl acetate; *dl*-Alpha tocopheryl acetate; *d*-Alpha tocopheryl acid succinate; *dl*-Alpha tocopheryl acid succinate; beta tocopherol; delta tocopherol; gamma tocopherol; tocopherols excipient.

d-Alpha tocopherol

Empirical formula: $C_{29}H_{50}O_2$
Molecular weight: 430.72
CAS number: [59-02-9]
Synonyms: natural alpha tocopherol; (+)-(2*R*,4′*R*,8′*R*)-2,5,7,8-tetramethyl-2-(4′,8′,12′-trimethyltridecyl)-6-chromanol; *d*-α-tocopherol; vitamin E.
Appearance: a practically odorless, clear, yellow, or greenish-yellow viscous oil.
Melting point: 2.5–3.5°C
Solubility: practically insoluble in water; soluble in ethanol (95%). Miscible with acetone, chloroform, ether, and vegetable oils.
Specific gravity: 0.95
Comments: *d*-alpha tocopherol is the naturally occurring form of alpha tocopherol.

d-Alpha tocopheryl acetate

Empirical formula: $C_{31}H_{52}O_3$
Molecular weight: 472.73
CAS number: [58-95-7]
Synonyms: (+)-(2*R*,4′*R*,8′*R*)-2,5,7,8-tetramethyl-2-(4′,8′,12′-trimethyltridecyl)-6-chromanyl acetate; *d*-α-tocopheryl acetate; vitamin E.
Appearance: a practically odorless, clear, yellow, or greenish-yellow colored viscous oil that may solidify in the cold.
Melting point: 28°C
Solubility: practically insoluble in water; soluble in ethanol (95%). Miscible with acetone, chloroform, ether, and vegetable oils.
Specific rotation $[\alpha]_D^{25}$: +0.25° (10% w/v solution in chloroform)
Comments: unstable to alkalis.

dl-Alpha tocopheryl acetate

Empirical formula: $C_{31}H_{52}O_3$
Molecular weight: 472.73
CAS number: [7695-91-2]
Synonyms: (±)-3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-6-ol acetate; (±)-(2*RS*,4′*RS*,8′*RS*)-2,5,7,8-tetramethyl-2-(4′,8′,12′-trimethyltridecyl)-6-chromanyl acetate; (±)-α-tocopherol acetate; α-tocopheroli acetas; all-*rac*-α-tocopheryl acetate; *dl*-α-tocopheryl acetate; vitamin E.

Appearance: a practically odorless, clear, yellow, or greenish-yellow viscous oil.
Density: 0.953 g/cm^3
Melting point: –27.5°C
Refractive index: n_D^{20} = 1.4950–1.4972
Solubility: practically insoluble in water; freely soluble in acetone, chloroform, ethanol, ether, and vegetable oils; soluble in ethanol (95%).
Comments: unstable to alkali. However, unlike alpha tocopherol, the acetate is much less susceptible to the effects of air, light, or ultraviolet light. Alpha tocopherol acetate concentrate, a powdered form of alpha tocopherol acetate, is described in the PhEur 2005. The concentrate may be prepared by either dispersing alpha tocopherol acetate in a suitable carrier such as acacia or gelatin, or by adsorbing alpha tocopherol acetate on silicic acid.

d-Alpha tocopheryl acid succinate

Empirical formula: $C_{33}H_{54}O_5$
Molecular weight: 530.8
CAS number: [4345-03-3]
Synonyms: (+)-α-tocopherol hydrogen succinate; *d*-α-tocopheryl acid succinate; vitamin E.
Appearance: a practically odorless white powder.
Melting point: 76–77°C
Solubility: practically insoluble in water; slightly soluble in alkaline solutions; soluble in acetone, ethanol (95%), ether, and vegetable oils; very soluble in chloroform.
Comments: unstable to alkalis.

dl-Alpha tocopheryl acid succinate

Empirical formula: $C_{33}H_{54}O_5$
Molecular weight: 530.8
CAS number: [17407-37-3]
Synonyms: (±)-α-tocopherol hydrogen succinate; *dl*-α-tocopheryl acid succinate; *dl*-α-tocopherol succinate; vitamin E.
Appearance: a practically odorless, white crystalline powder.
Solubility: practically insoluble in water; slightly soluble in alkaline solutions; soluble in acetone, ethanol (95%), ether, and vegetable oils; very soluble in chloroform.
Comments: unstable to alkalis.

Beta tocopherol

Empirical formula: $C_{28}H_{48}O_2$
Molecular weight: 416.66
CAS number: [148-03-8]
Synonyms: cumotocopherol; (±)-3,4-dihydro-2,5,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-β-benzopyran-6-ol; 5,8-dimethyltocol; neotocopherol; *dl*-β-tocopherol; vitamin E; *p*-xylotocopherol.
Appearance: a pale yellow-colored viscous oil.
Solubility: practically insoluble in water; freely soluble in acetone, chloroform, ethanol (95%), ether, and vegetable oils.
Specific rotation $[\alpha]_D^{20}$**:** +6.37°
Comments: less active biologically than alpha tocopherol. Obtained along with alpha tocopherol and gamma tocopherol from natural sources. Beta tocopherol is very stable to heat and alkalis and is slowly oxidized by atmospheric oxygen.

Delta tocopherol

Empirical formula: $C_{27}H_{46}O_2$
Molecular weight: 402.64
CAS number: [119-13-1]
Synonyms: (±)-3,4-dihydro-2,8-dimethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-6-ol; E309; 8-methyltocol; *dl*-δ-tocopherol; vitamin E.
Appearance: a pale yellow-colored viscous oil.
Solubility: practically insoluble in water; freely soluble in acetone, chloroform, ethanol (95%), ether, and vegetable oils.
Comments: occurs naturally as 30% of the tocopherol content of soybean oil. Delta tocopherol is said to be the most potent antioxidant of the tocopherols.

Gamma tocopherol

Empirical formula: $C_{28}H_{48}O_2$
Molecular weight: 416.66
CAS number: [7616-22-0]
Synonyms: (±)-3,4-dihydro-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-6-ol; 7,8-dimethyltocol; E308; *dl*-γ-tocopherol; vitamin E; *o*-xylotocopherol.
Appearance: a pale yellow-colored viscous oil.
Melting point: –30°C
Solubility: practically insoluble in water; freely soluble in acetone, chloroform, ethanol (95%), ether, and vegetable oils.
Specific rotation $[\alpha]_D^{20}$**:** –2.4° (in ethanol (95%))
Comments: occurs in natural sources along with alpha and beta tocopherol. Gamma tocopherol is biologically less active than alpha tocopherol. Very stable to heat and alkalis; slowly oxidized by atmospheric oxygen and gradually darkens on exposure to light.

Tocopherols excipient

Synonyms: *Embanox tocopherol.*
Appearance: a pale yellow-colored viscous oil.
Comments: tocopherols excipient is described in the USPNF 23 as a vegetable oil solution containing not less than 50.0% of total tocopherols, of which not less than 80.0% consists of varying amounts of beta, delta, and gamma tocopherols.

18 Comments

Note that most commercially available tocopherols are used as sources of vitamin E, rather than as antioxidants in pharmaceutical formulations.

Various mixtures of tocopherols, and mixtures of tocopherols with other excipients, are commercially available and individual manufacturers should be consulted for specific information on their products. The EINECS number for α-tocopherol is 215-798-8. The EINECs number for *d*-α-tocopherol is 200-412-2; and the EINECS number for *dl*-α-tocopherol is 233-466-0.

19 Specific References

1 Nielsen PB, Müllertz A, Norling T, Kristensen HG. The effect of α-tocopherol on the *in vitro* solubilisation of lipophilic drugs. *Int J Pharm* 2001; **222**: 217–224.
2 Constantinides PP, Tustian A, Kessler DR. Tocol emulsions for drug solubilization and parenteral delivery. *Adv Drug Delivery* 2004; **56**(9): 1243–1255.
3 Strickley RG. Solubilizing excipients in oral and injectable formulations. *Pharm Res* 2004; **21**(2): 201–230.

4 Johnson DM, Gu LC. Autoxidation and antioxidants. In: Swarbrick J, Boylan JC, eds. *Encyclopedia of Pharmaceutical Technology*, volume **1**. New York: Marcel Dekker, 1988: 415–450.
5 Allwood MC. Compatibility and stability of TPN mixtures in big bags. *J Clin Hosp Pharm* 1984; **9**: 181–198.
6 Buck DF. Antioxidants. In: Smith J, ed. *Food Additive User's Handbook*. Glasgow: Blackie, 1991: 1–46.
7 Rudy BC, Senkowski BZ. *dl*-Alpha-tocopheryl acetate. In: Florey K, ed. *Analytical Profiles of Drug Substances*, volume **3**. New York: Academic Press, 1974: 111–126.
8 FAO/WHO. Evaluation of certain food additives and contaminants. Thirtieth report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1987; No. 751.

20 General References

US National Research Council Food and Nutrition Board. *Recommended Dietary Allowances*, 10th edn. Washington DC: National Academy Press, 1989: 99–105.

21 Authors

SC Owen.

22 Date of Revision

4 August 2005.

Aluminum Hydroxide Adjuvant

1 Nonproprietary Names

PhEur: Aluminii hydroxidum hydricum ad adsorptionem

2 Synonyms

Alhydrogel; aluminium hydroxide adjuvant; aluminium oxyhydroxide; poorly crystalline boehmite; pseudoboehmite; *Rehydragel*.

3 Chemical Name and CAS Registry Number

Aluminum oxyhydroxide [21645-51-2]

4 Empirical Formula and Molecular Weight

AlO(OH) 59.99

5 Structural Formula

Structural hydroxyl groups form hydrogen bonds between AlO(OH) octahedral sheets, where hydroxyl groups are exposed at the surface. The surface hydroxyl groups produce a pH-dependent surface charge by accepting a proton to produce a positive site, or donating a proton to produce a negative site. The pH-dependent surface charge is characterized by the point of zero charge, which is equivalent to the isoelectric point in protein chemistry. The surface hydroxyl groups may also undergo ligand exchange with fluoride, phosphate, carbonate, sulfate, or borate anions.

6 Functional Category

Adsorbent; vaccine adjuvant.

7 Applications in Pharmaceutical Formulation or Technology

Aluminum hydroxide adjuvant is used in parenteral human and veterinary vaccines.(1) It activates T_H2 immune responses, including IgG and IgE antibody responses. It is also used for the isolation of certain serum components such as blood clotting factors.(2)

8 Description

Aluminum hydroxide adjuvant is a white hydrogel that sediments slowly and forms a clear supernatant.

9 Pharmacopeial Specifications

See Table I. Note that the USP 28 includes a monograph for aluminum hydroxide gel, which is a form of aluminum hydroxide that is used as an antacid, in which there is a partial substitution of carbonate for hydroxide.

See Section 17.

Table I: Pharmacopeial specifications for aluminum hydroxide adjuvant.

Test	PhEur 2005
Identification	+
Characters	+
Solution	+
pH	5.5–8.5
Adsorption power	+
Sedimentation	+
Chlorides	$\leqslant$0.33%
Nitrates	$\leqslant$100 ppm
Sulfates	$\leqslant$0.5%
Ammonium	$\leqslant$50 ppm
Arsenic	$\leqslant$1 ppm
Iron	$\leqslant$10 ppm
Heavy metals	$\leqslant$20 ppm
Bacterial endotoxins	+
Assay	90.0–110.0%

10 Typical Properties

Acidity/alkalinity: pH = 5.5–8.5

Particle size distribution: primary particles are fibrous with average dimensions of 4.5 × 2.2 × 10 nm. The primary particles form aggregates of 1–10 μm.

Point of zero charge: pH = 11.4

Protein binding capacity: >0.5 mg BSA/mg equivalent Al_2O_3

Solubility: soluble in alkali hydroxides and mineral acids. Heat may be required to dissolve the aluminum hydroxide adjuvant.

Specific surface area: 500 m^2/g.(3)

X-ray diffractogram: exhibits characteristic x-ray diffraction pattern having diffraction bands at 6.46, 3.18, 2.35, 1.86, 1.44 and 1.31 Å.

11 Stability and Storage Conditions

Aluminum hydroxide adjuvant is stable for at least two years when stored at 4–30°C in well-sealed inert containers. It must not be allowed to freeze as the hydrated colloid structure will be irreversibly damaged.

12 Incompatibilities

When exposed to phosphate, carbonate, sulfate, or borate anions, the point of zero charge for aluminum hydroxide adjuvant decreases.

13 Method of Manufacture

Aluminum hydroxide adjuvant is prepared by the precipitation of a soluble aluminum salt by an alkali hydroxide, or the precipitation of an alkali aluminate by acid.

14 Safety

Aluminum hydroxide adjuvant is intended for use in parenteral vaccines and is generally regarded as nontoxic. It may cause mild irritation, dryness, and dermatitis on skin contact. On eye contact, aluminum hydroxide adjuvant may also cause redness, conjunctivitis, and short-term mild irritation. Ingestion of large amounts may cause gastrointestinal irritation with nausea, vomiting, and constipation. Inhalation of the dried product may cause respiratory irritation and cough. Type I hypersensitivity reactions following parenteral administration have been reported.(4)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16 Regulatory Status

GRAS listed. Accepted for use in human and veterinary parenteral vaccines in Europe and the USA. The limits for use in human vaccines are 0.85 mg aluminum/dose (FDA) and 1.25 mg aluminum/dose (WHO). There are no established limits for use in veterinary vaccines. Reported in the EPA TSCA Inventory.

17 Related Substances

Aluminum phosphate adjuvant.

18 Comments

Different grades of aluminum hydroxide adjuvant with various concentrations, protein binding capacities, and points of zero charge are available.

The impurity limits at 2% equivalent Al_2O_3 are $Cl < 0.5\%$; $SO_4 < 0.5\%$; $PO_4 < 0.1\%$; $NO_3 < 0.1\%$; $NH_4 < 0.1\%$; $Fe < 20$ ppm; $As < 0.6$ ppm; and heavy metals < 20 ppm.

The aluminum hydroxide gel referred to in the USP 28 is used in cosmetics as an emollient, filler, humectant, a mild astringent, and viscosity controlling agent. In pharmaceutical preparations it is used as an adsorbent, and as a protein binder.(5) It is also used therapeutically as an antacid, and as an abrasive in dentrifrices. It is not, however, used as a vaccine adjuvant.

19 Specific References

1 Shirodkar S, Hutchinson RL, Perry DL, *et al*. Aluminum compounds used as adjuvants in vaccines. *Pharm Res* 1990; **7**: 1282–1288.

2 Prowse CV, Griffin B, Pepper DS, *et al*. Changes in factor VIII complex activities during the production of a clinical intermediate purity factor VIII concentrate. *Thromb Haemost* 1981; **46**: 597–601.

3 Johnston CT, Wang JL, Hem SL. Measuring the surface area of aluminum hydroxide adjuvant. *J Pharm Sci* 2002; **91**: 1702–1706.

4 Goldenthal KL, Cavagnaro JA, Alving G, Vogel FR. Safety evaluation of vaccine adjuvants. *AIDS Res Hum Retroviruses* 1993: **9** (Suppl. 1): 547–551.

5 Ash M, Ash I. *Handbook of Pharmaceutical Additives*, 2nd edn. Endicott, NY: Synapse Information Resources, 2002: 298.

20 General References

Gupta RK, Rost BE, Relyveld E, Siber GR. Adjuvant properties of aluminum and calcium compounds. In: Powell MF, Newman MJ, eds. *Vaccine Design*. New York: Plenum, 1995: 229–248.

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21 Authors

SL Hem, PB Klepak, EB Lindblad.

22 Date of Revision

2 September 2005.

Aluminum Oxide

1 Nonproprietary Names

None adopted.

2 Synonyms

Activated alumina; activated aluminum oxide; alpha aluminum oxide; alumina; alumina, activated; alumina, calcined; alumina, tabular; aluminum oxide alumite; aluminum trioxide.

3 Chemical Name and CAS Registry Number

Aluminum oxide [1344-28-1]

4 Empirical Formula and Molecular Weight

Al_2O_3 101.96

5 Structural Formula

Aluminum oxide occurs naturally as the minerals bauxite, bayerite, boehmite, corundum, diaspore, and gibbsite.

6 Functional Category

Adsorbent; dispersing agent.

7 Applications in Pharmaceutical Formulation or Technology

Aluminum oxide is used mainly in tablet formulations.(1) It is used for decoloring powders and is particularly widely used in antibiotic formulations. It is also used in suppositories, pessaries, and urethral inserts. Hydrated aluminum oxide (*see* Section 18) is used in mordant dyeing to make lake pigments, in cosmetics, and therapeutically as an antacid.

8 Description

Aluminum oxide occurs as a white crystalline powder. Aluminum oxide occurs as two crystalline forms. α-aluminum oxide is composed of colorless hexagonal crystals, and γ-aluminum oxide is composed of minute colorless cubic crystals that are transformed to the α-form at high temperatures.

9 Pharmacopeial Specifications

See Section 18.

10 Typical Properties

Boiling point: 2977°C
Density (bulk): 0.9–1.1 g/cm^3
Flammability: nonflammable.
Hardness (Mohs): 8.8
Hygroscopicity: very hygroscopic.
Melting point: 2050°C
Solubility: slowly soluble in aqueous alkaline solutions; practically insoluble in nonpolar organic solvents, diethyl ether, ethanol (95%), and water.
Specific gravity: 2.8 (becomes 4.0 at 800°C)
Vapor pressure: 133.3 Pa at 2158°C

11 Stability and Storage Conditions

Aluminum oxide should be stored in a well-closed container in a cool, dry, place. It is very hygroscopic.

12 Incompatibilities

Aluminum oxide should be kept well away from water. It is incompatible with strong oxidizers and chlorinated rubber. Aluminum oxide also reacts with chlorine trifluoride, ethylene oxide, sodium nitrate, and vinyl acetate. Exothermic reactions above 200°C with halocarbon vapors produce toxic hydrogen chloride and phosgene fumes.

13 Method of Manufacture

Most of the aluminum oxide produced commercially is obtained by the calcination of aluminum hydroxide.

14 Safety

Aluminum oxide is generally regarded as relatively nontoxic and nonirritant when used as an excipient. Inhalation of finely divided particles may cause lung damage (Shaver's disease).

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled.(2) In the UK, the occupational exposure limits for aluminum oxide are 10 mg/m^3 long-term (8-hour TWA) for total inhalable dust and 4 mg/m^3 for respirable dust.(3)

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral tablets and topical sponge). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

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18 Comments

A specification for aluminum oxide is included in Japanese Pharmaceutical Excipients 2004 (JPE), *see* Table I. A specification for light aluminum oxide is also included. The PhEur 2005 includes a specification for hydrated aluminum oxide that contains the equivalent of 47.0–60.0% of Al_2O_3. The EINECS number for aluminum oxide is 215-691-6.

Table I: JPE specification for aluminum oxide.[4]

Test	JPE 2004
Identification	+
Water-soluble substances	+
Heavy metals	⩽30 ppm
Lead	⩽30 ppm
Arsenic	⩽5 ppm
Loss on drying	⩽1.5%
Loss on ignition	⩽2.5%
Assay	⩾96.0%

19 Specific References

1 Rupprecht H. Processing of potent substances with inorganic supports by imbedding and coating. *Acta Pharm Technol* 1980; **26**: 13–27.

2 National Poisons Information Service (1997). Aluminium oxide. http://www.intox.org/databank/documents/chemical/alumoxde/ukpid33.htm (accessed 25 April 2005).

3 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.

4 Japan Pharmaceutical Excipients Council. *Japanese Pharmaceutical Excipients 2004*. Tokyo: Yakuji Nippo, 2004: 67–68.

20 General References

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21 Authors

LY Galichet.

22 Date of Revision

17 August 2005.

Aluminum Phosphate Adjuvant

1 Nonproprietary Names

None adopted.

2 Synonyms

Aluminum hydroxyphosphate; aluminium hydroxyphosphate; *Adju-Phos*; *Rehydraphos*.

3 Chemical Name and CAS Registry Number

Aluminum phosphate [7784-30-7]

4 Empirical Formula and Molecular Weight

$Al(OH)_x(PO_4)_y$

The molecular weight is dependent on the degree of substitution of phosphate groups for hydroxyl groups.

5 Structural Formula

Aluminum phosphate adjuvant occurs as a precipitate of amorphous aluminum hydroxide in which some sites contain phosphate groups instead of hydroxyl. Both hydroxyl and phosphate groups are exposed at the surface. The hydroxyl groups produce a pH-dependent surface charge by accepting a proton to produce a positive site, or donating a proton to produce a negative site. The pH-dependent surface charge is characterized by the point of zero charge, which is equivalent to the isoelectric point in protein chemistry. The surface hydroxyl groups may also undergo ligand exchange with fluoride, phosphate, carbonate, sulfate, or borate groups.

Aluminum phosphate adjuvant is not a stoichiometric compound. Rather, the degree of phosphate group substitution for hydroxyl groups depends on the precipitation recipe and conditions.

6 Functional Category

Adsorbent; vaccine adjuvant.

7 Applications in Pharmaceutical Formulation or Technology

Aluminum phosphate adjuvant is used in parenteral human and veterinary vaccines.(1) It activates T_H2 immune responses, including IgG and IgE antibody responses.

8 Description

Aluminum phosphate adjuvant is a white hydrogel that sediments slowly and forms a clear supernatant.

9 Pharmacopeial Specifications

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10 Typical Properties

Acidity/alkalinity: 6.0–8.0

Al : P atomic ratio: 1.1–1.15 : 1.0

Aluminum (%): 0.5–0.75

Particle size distribution: primary particles are platy with an average diameter of 50 nm. The primary particles form aggregates of 1–10 μm.

Point of zero charge: pH = 4.6–5.6, depending on the Al : P atomic ratio.

Protein binding capacity: >0.6 mg lysozyme/mg equivalent Al_2O_3

Solubility: soluble in mineral acids and alkali hydroxides.

X-ray diffractogram: amorphous to x-rays.

11 Stability and Storage Conditions

Aluminum phosphate adjuvant is stable for at least six months when stored at 4–30°C in well-sealed inert containers. It must not be allowed to freeze as the hydrated colloid structure will be irreversibly damaged.

12 Incompatibilities

The point of zero charge is related directly to the Al : P atomic ratio. Therefore, the substitution of additional phosphate groups for hydroxyl groups will lower the point of zero charge. Substitution of carbonate, sulfate, or borate ions for hydroxyl groups will also affect the point of zero charge.

13 Method of Manufacture

Aluminum phosphate adjuvant is formed by the reaction of a solution of aluminum chloride and phosphoric acid with alkali hydroxide.

14 Safety

Aluminum phosphate adjuvant is intended for use in parenteral vaccines and is generally regarded as safe. It may cause mild irritation, dryness, and dermatitis on skin contact. It may also cause redness, conjunctivitis, and short-term mild irritation on eye contact. Ingestion of large amounts of aluminum phosphate adjuvant may cause respiratory irritation with nausea, vomiting, and constipation. Inhalation is unlikely, although the dried product may cause respiratory irritation and cough. Type I hypersensitivity reactions following parenteral administration have also been reported.(2)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16 Regulatory Status

GRAS listed. Accepted for use in human and veterinary vaccines in Europe and the USA. The limits for use in human vaccines are 0.85 mg aluminum/dose (FDA) and 1.25 mg aluminum/dose (WHO). There are no established limits for use in veterinary vaccines. Reported in the EPA TSCA Inventory.

17 Related Substances

Aluminum hydroxide adjuvant.

18 Comments

The USP 28 monograph for aluminum phosphate ($ALPO_4$) gel describes aluminum phosphate, which is used as an antacid, not as a vaccine adjuvant.

19 Specific References

1 Shirodkar S, Hutchinson RL, Perry DL, *et al.* Aluminum compounds used as adjuvants in vaccines. *Pharm Res* 1990; **7**: 1282–1288.

2 Goldenthal KL, Cavagnaro JA, Alving G, Vogel FR. Safety evaluation of vaccine adjuvants. *AIDS Res Hum Retroviruses* 1993: **9** (Suppl. 1): 547–551.

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Lindblad EB. Aluminum adjuvants – in retrospect and prospect. *Vaccine* 2004; **22**: 3658–3668.

Lindblad EB. Aluminum adjuvants. In: Stewart-Tull DES, ed. *The Theory and Practical Application of Adjuvants*. New York: Wiley, 1995: 21–35.

Vogel FR, Hem SL. Immunogenic adjuvants. In: Plotkin SA, Orenstein WA, eds. *Vaccines*, 4th edn. New York: W.B. Saunders, 2003.

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21 Authors

SL Hem, PB Klepak, EB Lindblad.

22 Date of Revision

2 September 2005.

Aluminum Stearate

1 Nonproprietary Names

None adopted.

2 Synonyms

Octadecanoic acid aluminum salt; stearic acid aluminum salt.

3 Chemical Name and CAS Registry Number

Aluminum tristearate [637-12-7]

4 Empirical Formula and Molecular Weight

$C_{54}H_{105}AlO_6$ 877.39

5 Structural Formula

$[CH_3(CH_2)_{16}COO]_3Al$

6 Functional Category

Emollient; emulsion stabilizer; gelling agent; opacifier; stabilizing agent.

7 Applications in Pharmaceutical Formulation or Technology

Aluminum stearate is mainly used in microencapsulation(1–3) and in the manufacture of ointments. It is also used in cosmetics such as mascara, moisturizers, and sunscreens.

It should be noted that aluminum stearate can also refer to the distearate (CAS number [300-92-5]) and the monostearate (CAS number [7047-84-9]) in addition to the tristearate. The distearate exhibits the same excipient properties as the tristearate and is used in similar pharmaceutical applications. However, the monostearate is more widely used in cosmetics as a colorant.

8 Description

Aluminum stearate occurs as a white, fine, bulky powder with a slight odor of fatty acid. It is a hard material.

9 Pharmacopeial Specifications

See Section 18.

10 Typical Properties

Melting point: 117–120°C
Solubility: practically insoluble in water. Soluble in ethanol (95%), benzene, turpentine oil, and mineral oils when freshly prepared.
Specific gravity: 1.01

11 Stability and Storage Conditions

Aluminum stearate should be stored in a well-closed container in a cool, dry, place. It is stable under ordinary conditions of use and storage.

12 Incompatibilities

—

13 Method of Manufacture

Aluminum stearate is prepared by reacting aluminum with stearic acid.

14 Safety

Aluminum stearate is generally regarded as relatively nontoxic and nonirritant when used as an excipient.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled. When heated to decomposition, aluminum stearate emits acrid smoke and irritating vapors.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets, topical creams and ointments). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Aluminum distearate; aluminum monostearate.

Aluminum distearate

Empirical formula: $C_{36}H_{71}O_5 \cdot Al$
Molecular weight: 610.9
CAS number: [300-92-5]
Synonyms: hydroxyaluminum distearate; aluminum stearate; aluminum monobasic stearate
Description: aluminum distearate occurs as a fine white to off-white colored powder with a slight odor of fatty acid.
Melting point: 150–165°C
Specific gravity: 1.01
Solubility: soluble in benzene, and in ethanol (95%); practically insoluble in water.
Comments: the EINECS number for aluminum distearate is 206-101-8.

Aluminum monostearate

Empirical formula: $C_{18}H_{37}O_4Al$
Molecular weight: 344.5
CAS number: [7047-84-9]
Synonyms: dihydroxyaluminum monostearate; aluminum stearate; aluminum, dihydroxy (octadecanoato-O-); stearic acid aluminum dihydroxide salt.

Melting point: 220–225°C
Specific gravity: 1.14
Solubility: soluble in benzene, and in ethanol (95%); practically insoluble in water.
Comments: the EINECS number for aluminum monostearate is 230-325-5.

18 Comments

A specification for aluminum stearate, described as consisting mainly of the distearate, is included in the Japanese Pharmaceutical Excipients 2004 (JPE), *see* Table I. The EINECS number for aluminum tristearate is 211-279-5.

Table I: JPE specifications for aluminum stearate.[4]

Test	JPE 2004
Identification	+
Acid value of fatty acid	+
Free fatty acid	+
Soluble salt	+
Heavy metals	⩽20 ppm
Lead	⩽20 ppm
Arsenic	⩽2 ppm
Loss on drying	⩽2.0%
Assay (of Al)	4.0–6.0%

19 Specific References

1 Horoz BB, Kilicarslan M, Yuksel N, *et al*. Effect of different dispersing agents on the characteristics of *Eudragit* microspheres prepared by a solvent evaporation method. *J Microencapsul* 2004; **21**: 191–202.
2 Wu PC, Huang YB, Chang JI, *et al*. Preparation and evaluation of sustained release microspheres of potassium chloride prepared with ethylcellulose. *Int J Pharm* 2003; **260**: 115–121.
3 Wu PC, Huang YB, Chang JS, *et al*. Design and evaluation of sustained release microspheres of potassium chloride prepared by *Eudragit*. *Eur J Pharm Sci* 2003; **19**: 115–122.
4 Japan Pharmaceutical Excipients Council. *Japanese Pharmaceutical Excipients 2004*. Tokyo: Yakuji Nippo, 2004: 74–75.

20 General References

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21 Authors

LY Galichet.

22 Date of Revision

17 August 2005.

Ammonia Solution

1 Nonproprietary Names

BP: Ammonia solution, concentrated
PhEur: Ammoniae solution concentrata
USPNF: Strong ammonia solution

2 Synonyms

Ammoniaca; ammoniacum; aqua ammonia; concentrated ammonia solution; spirit of hartshorn; stronger ammonia water.

3 Chemical Name and CAS Registry Number

Ammonia [7664-41-7]

4 Empirical Formula and Molecular Weight

NH_3 17.03

5 Structural Formula

NH_3

6 Functional Category

Alkalizing agent.

7 Applications in Pharmaceutical Formulation or Technology

Ammonia solution is typically not used undiluted in pharmaceutical applications. Generally, it is used as a buffering agent or to adjust the pH of solutions. Most commonly, ammonia solution (the concentrated form) is used to produce more dilute ammonia solutions.

Therapeutically, dilute ammonia solution is used as a reflex stimulant in 'smelling salts', as a rubefacient, and as a counterirritant to neutralize insect bites or stings.(1)

8 Description

Strong ammonia solution occurs as a clear, colorless liquid having an exceedingly pungent, characteristic odor. The PhEur 2005 states that concentrated ammonia solution contains not less than 25.0% and not more than 30.0% w/w of ammonia (NH_3). The USPNF 23 states that strong ammonia solution contains not less than 27.0% and not more than 31.0% w/w of ammonia (NH_3).

See also Section 17.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for ammonia solution.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Oxidizable substances	+	+
Pyridine and related substances	⩽2 ppm	—
Carbonates	⩽60 ppm	—
Chlorides	⩽1 ppm	—
Sulfates	⩽5 ppm	—
Iron	⩽0.25 ppm	—
Heavy metals	⩽1 ppm	⩽0.0013%
Residue on evaporation	⩽0.02 g/L	—
Limit of nonvolatile residue	—	⩽0.05%
Assay (of NH_3)	25.0–30.0%	27.0–31.0%

10 Typical Properties

Solubility: miscible with ethanol (95%) and water.
Specific gravity: 0.892–0.910

11 Stability and Storage Conditions

On exposure to the air, ammonia solution rapidly loses ammonia. Ammonia solution should be stored in a well-closed container, protected from the air, in a cool, dry place. The storage temperature should not exceed 20°C.

12 Incompatibilities

Ammonia solution reacts vigorously with sulfuric acid or other strong mineral acids and the reaction generates considerable heat; the mixture boils.

13 Method of Manufacture

Ammonia is obtained commercially chiefly by synthesis from its constituent elements, nitrogen and hydrogen, which are combined under high pressure and temperature in the presence of a catalyst. Ammonia solution is produced by dissolving ammonia gas in water.

14 Safety

Ingestion of strong solutions of ammonia is very harmful and causes severe pain in the mouth, throat, and gastrointestinal tract as well as severe local edema with cough, vomiting, and shock. Burns to the esophagus and stomach may result in perforation. Inhalation of the vapor causes sneezing, coughing, and, in high concentration, pulmonary edema. Asphyxia has been reported. The vapor is irritant to the eyes. Strong solutions are harmful when applied to the conjunctiva and mucous membranes. Topical application of even dilute ammonia solutions, used to treat insect bites, has caused burns, particularly when used with a subsequent dressing.(2–4)

When used as an excipient, ammonia solution is generally present in a formulation in a highly diluted form.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Care should be used in handling strong or concentrated ammonia solutions because of the caustic nature of the solution and the irritating properties of its vapor. Before containers are opened, they should be well cooled. The closure should be covered with a cloth or similar material while opening. Ammonia solution should not be tasted and inhalation of the vapor should be avoided. Ammonia solution should be handled in a fume cupboard. Eye protection, gloves, and a respirator are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral suspensions, topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Dilute ammonia solution.

Dilute ammonia solution

Synonyms: ammonia water.
Specific gravity: 0.95–0.96
Comments: several pharmacopeias include monographs for dilute ammonia solution. The JP 2001, for example, states that ammonia water contains not less than 9.5% and not more than 10.5% w/v of ammonia (NH_3).

18 Comments

Where 'ammonia solution' is prescribed therapeutically, dilute ammonia solution should be dispensed or supplied.

The EINECS number for ammonia solution is 231-635-3.

19 Specific References

1 Frohman IG. Treatment of physalia stings. *J Am Med Assoc* 1996; **197**: 733.
2 Beare JD, Wilson RS, Marsh RJ. Ammonia burns of the eye: an old weapon in new hands. *Br Med J* 1988; **296**: 590.
3 Payne MP, Delic JI. Ammonia. In: *Toxicity Review 24*. London: HMSO, 1991: 1–12.
4 Leduc D, Gris P, Lheureux P, *et al*. Acute and long term respiratory damage following inhalation of ammonia. *Thorax* 1992; **47**: 755–757.

20 General References

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21 Authors

PJ Sheskey.

22 Date of Revision

12 August 2005.

Ammonium Alginate

1 Nonproprietary Names

None adopted.

2 Synonyms

Alginic acid, ammonium salt; ammonium polymannuronate; E404; *Keltose*.

3 Chemical Name and CAS Registry Number

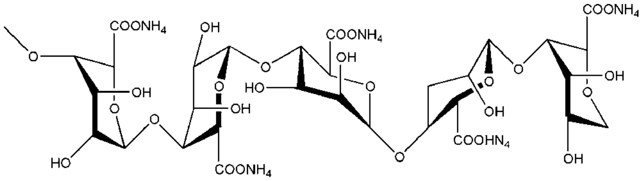
Ammonium alginate [9005-34-9]

4 Empirical Formula and Molecular Weight

$(C_6H_{11}NO_6)_n$ 193.16 (calculated)
217 (actual, average)

Ammonium alginate is the ammonium salt of alginic acid.

5 Structural Formula



The number and sequence of the mannuronate and glucuronate residues shown above vary in the naturally occurring alginate. The associated water molecules are not shown.

6 Functional Category

Diluent; emulsifier; film-former; humectant; stabilizer; thickener; thickening agent.

7 Applications in Pharmaceutical Formulation or Technology

Ammonium alginate is widely used in foods as a stabilizer, thickener and emulsifier. It is also used in pharmaceutical preparations as a color-diluent, emulsifier, film-former, and humectant.

8 Description

Ammonium alginate occurs as white to yellowish brown filamentous, grainy, granular, or powdered forms.

9 Pharmacopeial Specifications

See Section 18.

10 Typical Properties

Solubility: dissolves slowly in water to form a viscous solution; insoluble in ethanol and in ether.
Moisture content: not more than 15% at 105°C for 4 hours.

11 Stability and Storage Conditions

Ammonium alginate is a hygroscopic material, although it is stable if stored at low relative humidities and cool temperatures.

12 Incompatibilities

Incompatible with oxidizing agents and strong acids and alkalis.

13 Method of Manufacture

—

14 Safety

Ammonium alginate is widely used in cosmetics and food products, and also in pharmaceutical formulations such as tablets. It is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may be harmful.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled. Eye protection, gloves, and a dust respirator are recommended.

16 Regulatory Status

GRAS listed. Accepted in Europe for use as a food additive. Included in the FDA Inactive Ingredients Guide (oral, tablets).

17 Related Substances

Alginic acid; calcium alginate; potassium alginate; propylene glycol alginate; sodium alginate.

18 Comments

Alginates are commonly used in wound dressings.(1) Chitosan and alginates have been used together to produce sponges for use as wound dressings, or matrices for tissue engineering.(2) Alginate microspheres have been produced by internal gelation using emulsification methods.(3)

Although not included in any pharmacopeias, a specification for ammonium alginate is contained in the Food Chemicals Codex (FCC), *see* Table I.

Table I: FCC specification for ammonium alginate.(4)

Test	FCC 1996(4)
Identification	+
Arsenic	⩽3 mg/kg
Ash	⩽4.0% after drying
Heavy metals (as Pb)	⩽0.002%
Lead	⩽5 mg/kg
Loss on drying	⩽15.0%
Assay	18.0–21.0% of CO_2, corresponding to 88.7–103.6% ammonium alginate

19 Specific References

1 Morgan D. Wounds—what should a dressing formulary include? *Hosp Pharm* 2002; **9**(9): 261–266.

2 Lai HL, Abu' Khalil A, Craig DQ. The preparation and characterization of drug-loaded alginate and chitosan sponges. *Int J Pharm* 2003; **251**(1–2): 175–181.

3 Chan LW, Lee HY, Heng PW. Production of alginate microspheres by internal gelation using an emulsification method. *Int J Pharm* 2002; **242**(1–2): 259–262.

4 *Food Chemicals Codex*, 4th edn. Washington, DC: National Academy Press, 1996: 24.

20 General References

—

21 Authors

D Thassu, S Shah.

22 Date of Revision

15 August 2005.

Ascorbic Acid

1 Nonproprietary Names

BP: Ascorbic acid
JP: Ascorbic acid
PhEur: Acidum ascorbicum
USP: Ascorbic acid

2 Synonyms

C-97; cevitamic acid; 2,3-didehydro-L-*threo*-hexono-1,4-lactone; E300; 3-oxo-L-gulofuranolactone, enol form; vitamin C.

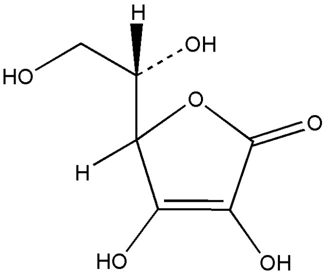
3 Chemical Name and CAS Registry Number

L-(+)-Ascorbic acid [50-81-7]

4 Empirical Formula and Molecular Weight

$C_6H_8O_6$ 176.13

5 Structural Formula



6 Functional Category

Antioxidant; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Ascorbic acid is used as an antioxidant in aqueous pharmaceutical formulations at a concentration of 0.01–0.1% w/v. Ascorbic acid has been used to adjust the pH of solutions for injection, and as an adjunct for oral liquids. It is also widely used in foods as an antioxidant. Ascorbic acid has also proven useful as a stabilizing agent in mixed micelles containing tetrazepam.(1)

8 Description

Ascorbic acid occurs as a white to light-yellow-colored, nonhygroscopic, odorless, crystalline powder or colorless crystals with a sharp, acidic taste. It gradually darkens in color upon exposure to light.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for ascorbic acid.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	—	+	—
Specific rotation (10% w/v solution)	+ 20.5° to + 21.5°	+ 20.5° to + 21.5°	+ 20.5° to + 21.5°
Residue on ignition	$\leqslant$0.10%	—	$\leqslant$0.1%
pH	2.2–2.5	2.1–2.6	—
Sulfated ash	—	$\leqslant$0.1%	—
Copper	—	$\leqslant$5 ppm	—
Heavy metals	$\leqslant$20 ppm	$\leqslant$10 ppm	$\leqslant$0.002%
Loss on drying	$\leqslant$0.20%	—	—
Iron	—	$\leqslant$2 ppm	—
Oxalic acid	—	+	—
Appearance of solution	+	+	—
Organic volatile impurities	—	—	+
Assay	$\geqslant$99.0%	99.0–100.5%	99.0–100.5%

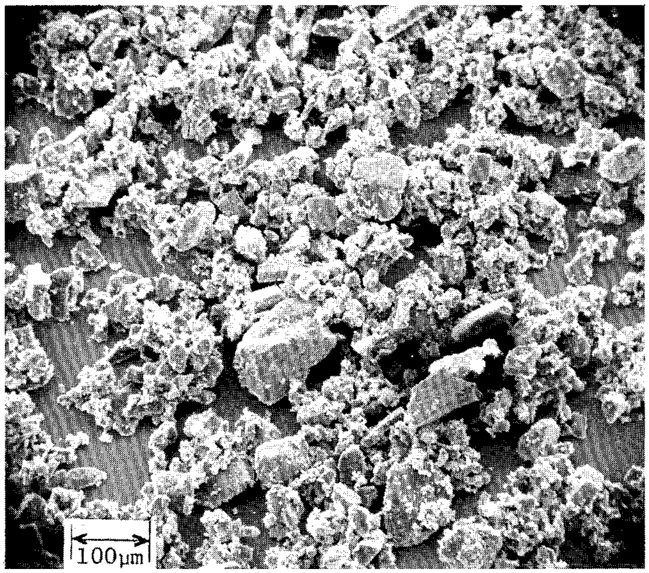
10 Typical Properties

Acidity/alkalinity: pH = 2.1–2.6 (5% w/v aqueous solution)
Density (bulk):
0.7–0.9 g/cm^3 for crystalline material;
0.5–0.7 g/cm^3 for powder.
Density (particle): 1.65 g/cm^3
Density (tapped):
1.0–1.2 g/cm^3 for crystalline material;
0.9–1.1 g/cm^3 for powder.
Density (true): 1.688 g/cm^3
Dissociation constant:
pK_{a1} = 4.17;
pK_{a2} = 11.57.
Melting point: 190°C (with decomposition)
Moisture content: 0.1% w/w
Solubility: *see* Table II.

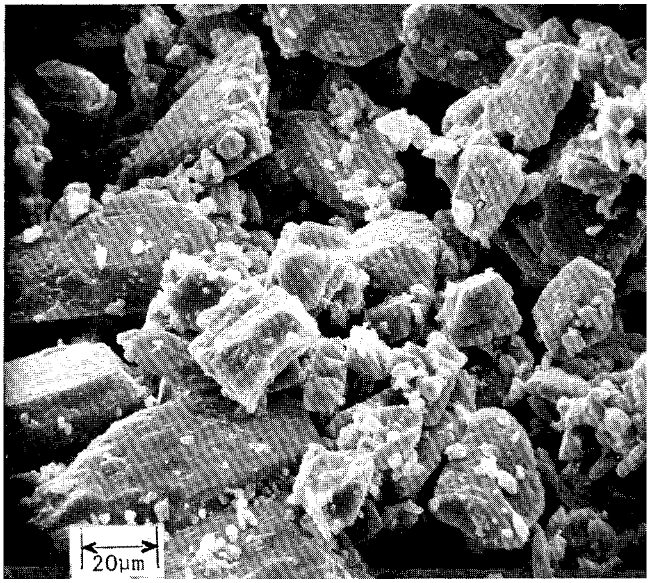
Table II: Solubility of ascorbic acid.

Solvent	Solubility at 20°C
Chloroform	Practically insoluble
Ethanol	1 in 50
Ethanol (95%)	1 in 25
Ether	Practically insoluble
Fixed oils	Practically insoluble
Glycerin	1 in 1000
Propylene glycol	1 in 20
Water	1 in 3.5

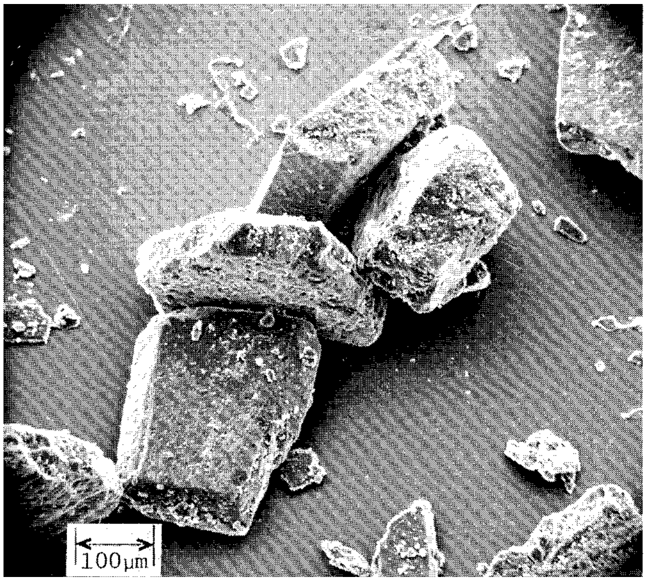
SEM: 1
Excipient: Ascorbic acid USP (fine powder)
Manufacturer: Pfizer Ltd
Lot No.: 9A-3/G92040-CO 146
Magnification: 120×
Voltage: 20 kV



SEM: 2
Excipient: Ascorbic acid USP (fine powder)
Manufacturer: Pfizer Ltd
Lot No.: 9A-3/G92040-CO 146
Magnification: 600×
Voltage: 20 kV



SEM: 3
Excipient: Ascorbic acid USP (fine granular)
Manufacturer: Pfizer Ltd
Lot No.: 9A-2/G01280-CO 148
Magnification: 120×
Voltage: 20 kV



11 Stability and Storage Conditions

In powder form, ascorbic acid is relatively stable in air. In the absence of oxygen and other oxidizing agents it is also heat stable. Ascorbic acid is unstable in solution, especially alkaline solution, readily undergoing oxidation on exposure to the air.(2,3) The oxidation process is accelerated by light and heat and is catalyzed by traces of copper and iron. Ascorbic acid solutions exhibit maximum stability at about pH 5.4. Solutions may be sterilized by filtration.

The bulk material should be stored in a well-closed nonmetallic container, protected from light, in a cool, dry place.

12 Incompatibilities

Incompatible with alkalis, heavy metal ions, especially copper and iron, oxidizing materials, methenamine, phenylephrine hydrochloride, pyrilamine maleate, salicylamide, sodium nitrite, sodium salicylate, theobromine salicylate, and picotamide.(4,5) Additionally, ascorbic acid has been found to interfere with certain colorimetric assays by reducing the intensity of the color produced.(6)

13 Method of Manufacture

Ascorbic acid is prepared synthetically or extracted from various vegetable sources in which it occurs naturally, such as rose hips, blackcurrants, the juice of citrus fruits, and the ripe fruit of *Capsicum annuum* L. A common synthetic procedure involves the hydrogenation of D-glucose to D-sorbitol, followed by oxidation using *Acetobacter suboxydans* to form L-sorbose. A carboxyl group is then added at C1 by air oxidation of the diacetone derivative of L-sorbose and the resulting diacetone-2-keto-L-gulonic acid is converted to L-ascorbic acid by heating with hydrochloric acid.

14 Safety

Ascorbic acid is an essential part of the human diet, with 40 mg being the recommended daily dose in the UK(7) and 60 mg in the US.(8) However, these figures are controversial, with some advocating doses of 150 or 250 mg daily. Megadoses of 10 g daily have also been suggested to prevent illness although such large doses are now generally considered to be potentially harmful.(9–11)

The body can absorb about 500 mg of ascorbic acid daily with any excess immediately excreted by the kidneys. Large doses may cause diarrhea or other gastrointestinal disturbances. Damage to the teeth has also been reported.(12) However, no adverse effects have been reported at the levels employed as an antioxidant in foods and pharmaceuticals. The WHO has set an acceptable daily intake of ascorbic acid, potassium ascorbate, and sodium ascorbate, as antioxidants in food, at up to 15 mg/kg body-weight in addition to that naturally present in food.(13)

LD_{50} (mouse, IV): 0.52 g/kg(14)
LD_{50} (mouse, oral): 3.37 g/kg
LD_{50} (rat, oral): 11.9 g/kg

15 Handling Precautions

Ascorbic acid may be harmful if ingested in large quantities and may be irritating to the eyes. Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and rubber or plastic gloves are recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (inhalations, injections, oral capsules, suspensions, tablets, topical preparations, and suppositories). Included in medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Ascorbyl palmitate; erythorbic acid; sodium ascorbate.

18 Comments

Many dosage forms for ascorbic acid have been developed for its administration to patients, including microencapsulation.(15)

A specification for ascorbic acid is contained in the Food Chemicals Codex (FCC).

The EINECS number for ascorbic acid is 200-066-2.

19 Specific References

1 Hammad MA, Muller BW. Solubility and stability of tetrazepam in mixed micelles. *Eur J Pharm Sci* 1998; **7**: 49–55.
2 Hajratwala BR. Stability of ascorbic acid. *STP Pharma* 1985; **1**: 281–286.
3 Touitou E, Gilhar D, Alhaique F, *et al*. Ascorbic acid in aqueous solution: bathochromic shift in dilution and degradation. *Int J Pharm* 1992; **78**: 85–87.
4 Botha SA, Lötter AP, du Preez JFL. DSC screening for drug–drug interactions in polypharmaceuticals intended for the alleviation of the symptoms of colds and flu. *Drug Dev Ind Pharm* 1987; **13**: 345–354.
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9 Ovesen L. Vitamin therapy in the absence of obvious deficiency: what is the evidence? *Drugs* 1984; **27**: 148–170.
10 Bates CJ. Is there a maximum safe dose of vitamin C (ascorbic acid)? *Br Med J* 1992; **305**: 32.
11 Mason P. Vitamin C. *Dietary Supplements*, 2nd edn. London: Pharmaceutical Press, 2001: 227–233.
12 Giunta JL. Dental erosion resulting from chewable vitamin C tablets. *J Am Dent Assoc* 1983; **107**: 253–256.
13 FAO/WHO. Toxicological evaluation of certain food additives with a review of general principles and of specifications. Seventeenth report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1974; No. 539.
14 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 309–310.
15 Esposito E, Cervellayi F, Menegatti E, *et al*. Spray-dried *Eudragit* microparticles as encapsulation devices for vitamin C. *Int J Pharm* 2002; **242**: 329–334.

20 General References

Abramovici B, Molard F, Seguin B, Gromenil JC. Comparative study of the tabletability of different grades of vitamin C [in French]. *STP Pharma* 1987; **3**: 16–22.
Allwood MC. Factors influencing the stability of ascorbic acid in total parenteral nutrition infusions. *J Clin Hosp Pharm* 1984; **9**: 75–85.
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Saleh SI, Stamm A. Contribution to the preparation of a directly compressible L-ascorbic acid granular form: comparison of granules prepared by three granulation methods and evaluation of their corresponding tablets. *STP Pharma* 1988; **4**: 182–187.
Seta Y, Higuchi F, Otsuka T, *et al*. Preparation and pharmacological evaluation of Captopril sustained-release dosage forms using oily semisolid matrix. *Int J Pharm* 1988; **41**: 255–262.

21 Authors

AH Kibbe.

22 Date of Revision

12 August 2005.

Ascorbyl Palmitate

1 Nonproprietary Names

BP: Ascorbyl palmitate
PhEur: Ascorbylis palmitas
USPNF: Ascorbyl palmitate

2 Synonyms

L-Ascorbic acid 6-palmitate; E304; 3-oxo-L-gulofuranolactone 6-palmitate; vitamin C palmitate.

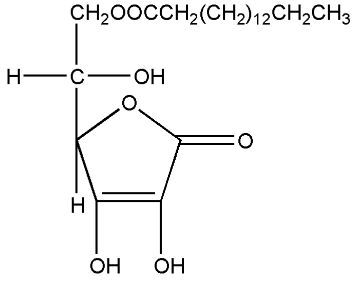
3 Chemical Name and CAS Registry Number

L-Ascorbic acid 6-hexadecanoate [137-66-6]

4 Empirical Formula and Molecular Weight

$C_{22}H_{38}O_7$ 414.54

5 Structural Formula



6 Functional Category

Antioxidant.

7 Applications in Pharmaceutical Formulation or Technology

Ascorbyl palmitate is primarily used either alone or in combination with alpha tocopherol as a stabilizer for oils in oral pharmaceutical formulations and food products; generally 0.05% w/v is used. It may also be used in oral and topical preparations as an antioxidant for drugs unstable to oxygen. The combination of ascorbyl palmitate with alpha tocopherol shows marked synergism, which increases the effect of the components and allows the amount used to be reduced.

The solubility of ascorbyl palmitate in alcohol permits it to be used in nonaqueous and aqueous systems and emulsions.

8 Description

Ascorbyl palmitate is a practically odorless, white to yellowish powder.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for ascorbyl palmitate.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Melting range	—	107–117°C
Specific rotation (10% w/v in methanol)	+21° to +24°	+21° to +24°
Loss on drying	$\leqslant$1.0%	$\leqslant$2.0%
Residue on ignition	—	$\leqslant$0.1%
Sulfated ash	$\leqslant$0.1%	—
Heavy metals	$\leqslant$10 ppm	$\leqslant$0.001%
Organic volatile impurities	—	+
Assay (dried basis)	98.0–100.5%	95.0–100.5%

10 Typical Properties

Solubility: *see* Table II.

Table II: Solubility of ascorbyl palmitate.

Solvent	Solubility at 20°C unless otherwise stated[1]
Acetone	1 in 15
Chloroform	1 in 3300
	1 in 11 at 60°C
Cottonseed oil	1 in 1670
Ethanol	1 in 8
	1 in 1.7 at 70°C
Ethanol (95%)	1 in 9.3
Ethanol (50%)	1 in 2500
Ether	1 in 132
Methanol	1 in 5.5
	1 in 1.7 at 60°C
Olive oil	1 in 3300
Peanut oil	1 in 3300
Propan-2-ol	1 in 20
	1 in 5 at 70°C
Sunflower oil	1 in 3300
Water	Practically insoluble
	1 in 500 at 70°C
	1 in 100 at 100°C

11 Stability and Storage Conditions

Ascorbyl palmitate is stable in the dry state, but is gradually oxidized and becomes discolored when exposed to light and high humidity. In an unopened container, stored in a cool place, it has a shelf life of at least 12 months. During processing, temperatures greater than 65°C should be avoided.

The bulk material should be stored in an airtight container at 8–15°C, protected from light.

12 Incompatibilities

Incompatibilities are known with oxidizing agents, e.g., in solution oxidation is catalyzed by trace metal ions such as Cu^{2+} and Fe^{3+}.

13 Method of Manufacture

Ascorbyl palmitate is prepared synthetically by the reaction of ascorbic acid with sulfuric acid followed by reesterification with palmitic acid.

14 Safety

Ascorbyl palmitate is used in oral pharmaceutical formulations and food products and is generally regarded as an essentially nontoxic and nonirritant material. The WHO has set an estimated acceptable daily intake for ascorbyl palmitate at up to 1.25 mg/kg body-weight.(2)

LD_{50} (mouse, oral): 25 g/kg(3)
LD_{50} (rat, oral): 10 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Ascorbyl palmitate dust may cause irritation to the eyes and respiratory tract. Eye protection is recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral, rectal, topical preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Ascorbic acid; sodium ascorbate.

18 Comments

The EINECS number for ascorbyl palmitate is 205-305-4.

In order to maximize the stability and efficacy of ascorbyl palmitate the following precautions are recommended: stainless steel, enamel, or glass should be used; deaeration (vacuum) procedures and inert gas treatment are recommended where feasible; protect from light and radiant energy.

The formation of ascorbyl palmitate vesicles (Aspasomes) and their pharmaceutical applications has recently been investigated.(4)

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3 Sweet DV, ed. *Registry of Toxic Effects of Chemical Substances*. Cincinnati: US Department of Health, 1987.
4 Gopinath D, Ravi D, Rao BR, *et al.* Ascorbyl palmitate vesicles (Aspasomes): formation, characterization and applications. *Int J Pharm* 2004; **271**: 95–113.

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Pongracz G. Antioxidant mixtures for use in food. *Int J Vitam Nutr Res* 1973; **43**: 517–525.

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21 Authors

PJ Weller.

22 Date of Revision

4 August 2005.

Aspartame

1 Nonproprietary Names

BP: Aspartame
PhEur: Aspartamum
USPNF: Aspartame

2 Synonyms

3-Amino-*N*-(α-carboxyphenethyl)succinamic acid *N*-methyl ester; 3-amino-*N*-(α-methoxycarbonylphenethyl)succinamic acid; APM; aspartyl phenylamine methyl ester; *Canderel*; E951; *Equal*; methyl *N*-α-L-aspartyl-L-phenylalaninate; *NutraSweet*; *Pal Sweet*; *Pal Sweet Diet*; *Sanecta*; SC-18862; *Tri-Sweet*.

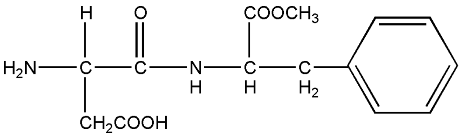
3 Chemical Name and CAS Registry Number

N-α-L-Aspartyl-L-phenylalanine 1-methyl ester [22839-47-0]

4 Empirical Formula and Molecular Weight

$C_{14}H_{18}N_2O_5$ 294.31

5 Structural Formula



6 Functional Category

Sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets,(1,2) powder mixes, and vitamin preparations. It enhances flavor systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose.

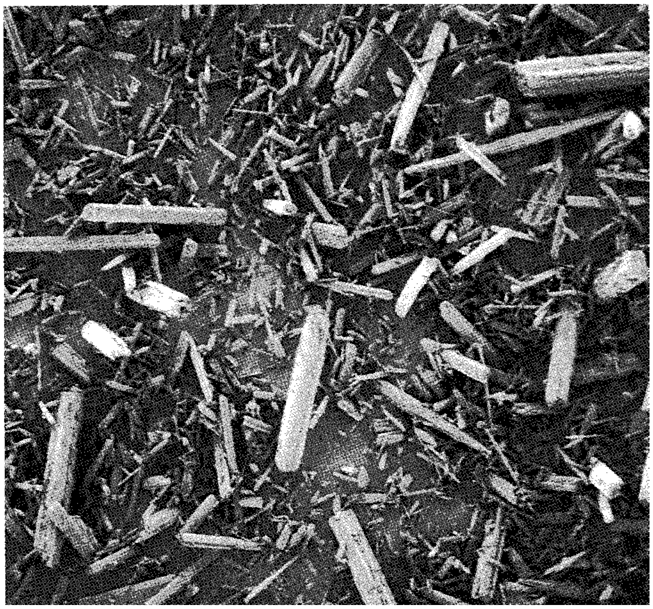
Unlike some other intense sweeteners, aspartame is metabolized in the body and consequently has some nutritive value: 1 g provides approximately 17 kJ (4 kcal). However, in practice, the small quantity of aspartame consumed provides a minimal nutritive effect.

Therapeutically, aspartame has also been used in the treatment of sickle cell anemia.(3)

8 Description

Aspartame occurs as an off white, almost odorless crystalline powder with an intensely sweet taste.

SEM: 1
Excipient: Aspartame
Magnification: 70×
Voltage: 3 kV



9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for aspartame.

Test	PhEur 2005	USPNF 23
Characters	+	—
Identification	+	+
Appearance of solution	+	—
Conductivity	⩽30 μS/cm	—
Specific optical rotation	+14.5° to +16.5°	+14.5° to +16.5°
Related substances	+	—
Heavy metals	⩽10 ppm	⩽0.001%
Loss on drying	⩽4.5%	⩽4.5%
Sulfated ash	⩽0.2%	⩽0.2%
Impurities	+	—
Transmittance	—	+
Limit of 5-benzyl-3,6-dioxo-2-piperazineacetic acid	—	⩽1.5%
Organic volatile impurities	—	+
Assay	98.0–102.0%	98.0–102.0%

10 Typical Properties

Acidity/alkalinity: pH = 4.5–6.0 (0.8% w/v aqueous solution).
Brittle fracture index: 1.05(4)

Bonding index:
0.8×10^2 (worst case)(4)
2.3×10^2 (best case)(4)
Flowability: 44% (Carr compressibility index)(4)
Density (bulk):
0.5–0.7 g/cm^3 for granular grade;
0.2–0.4 g/cm^3 for powder grade;
0.17 g/cm^3 (Spectrum Quality Products).(4)
Density (tapped): 0.29 g/cm^3 (Spectrum Quality Products)(4)
Density (true): 1.347 g/cm^3
Effective angle of internal friction: 43.0°(4)
Melting point: 246–247°C
Solubility: slightly soluble in ethanol (95%); sparingly soluble in water. At 20°C the solubility is 1% w/v at the isoelectric point (pH 5.2). Solubility increases at higher temperature and at more acidic pH, e.g., at pH 2 and 20°C solubility is 10% w/v.
Specific rotation $[\alpha]_D^{22}$: −2.3° in 1 N HCl

11 Stability and Storage Conditions

Aspartame is stable in dry conditions. In the presence of moisture, hydrolysis occurs to form the degradation products L-aspartyl-L-phenylalanine and 3-benzyl-6-carboxymethyl-2,5-diketopiperazine. A third-degradation product is also known, β-L-aspartyl-L-phenylalanine methyl ester. For the stability profile at 25°C in aqueous buffers, *see* Figure 1.

Stability in aqueous solutions has been enhanced by the addition of cyclodextrins,(5,6) and by the addition of polyethylene glycol 400 at pH 2.(7) However, at pH 3.5–4.5 stability is not enhanced by the replacement of water with organic solvents.(8)

Aspartame degradation also occurs during prolonged heat treatment; losses of aspartame may be minimized by using processes that employ high temperatures for a short time followed by rapid cooling.

The bulk material should be stored in a well-closed container, in a cool, dry place.

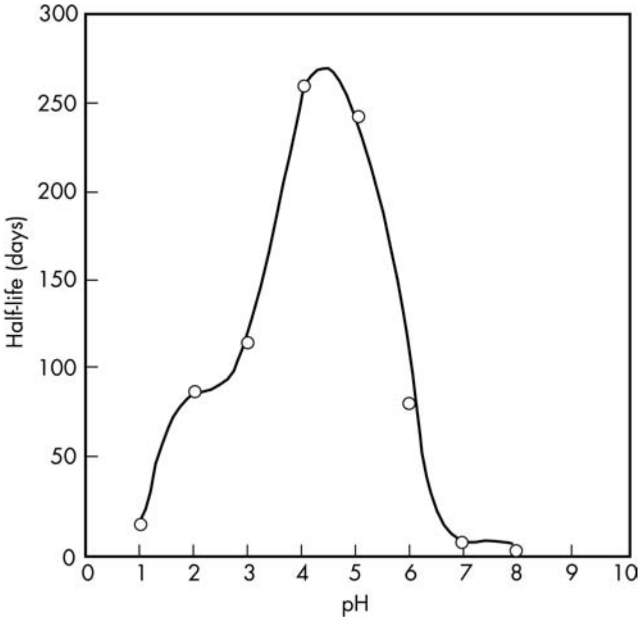


Figure 1: Stability profile of aspartame in aqueous buffers at 25°C.(9)

12 Incompatibilities

Differential scanning calorimetry experiments with some directly compressible tablet excipients suggests that aspartame is incompatible with dibasic calcium phosphate and also with the lubricant magnesium stearate.(10) Reactions between aspartame and sugar alcohols are also known.

13 Method of Manufacture

Aspartame is produced by coupling together L-phenylalanine (or L-phenylalanine methyl ester) and L-aspartic acid, either chemically or enzymatically. The former procedure yields both the sweet α-aspartame and nonsweet β-aspartame from which the α-aspartame has to be separated and purified. The enzymatic process yields only α-aspartame.

14 Safety

Aspartame is widely used in oral pharmaceutical formulations, beverages, and food products as an intense sweetener and is generally regarded as a nontoxic material. However, the use of aspartame has been of some concern owing to the formation of the potentially toxic metabolites methanol, aspartic acid, and phenylalanine. Of these materials, only phenylalanine is produced in sufficient quantities, at normal aspartame intake levels, to cause concern. In the normal healthy individual any phenylalanine produced is harmless, however it is recommended that aspartame be avoided or its intake restricted by those persons with phenylketonuria.(11)

The WHO has set an acceptable daily intake for aspartame at up to 40 mg/kg body-weight.(12) Additionally, the acceptable daily intake of diketopiperazine (an impurity found in aspartame) has been set by the WHO at up to 7.5 mg/kg body-weight.(13)

A number of adverse effects have been reported following the consumption of aspartame,(11,13) particularly in individuals who drink large quantities (up to 8 liters per day in one case) of aspartame-sweetened beverages. Reported adverse effects include: headaches;(14) grand mal seizure;(15) memory loss;(16) gastrointestinal symptoms; and dermatological symptoms.

Although aspartame has been reported to cause hyperactivity and behavioral problems in children, a double-blind controlled trial of 48 preschool-age children fed diets containing a daily intake of 38 ± 13 mg/kg body-weight of aspartame for 3 weeks showed no adverse effects attributable to aspartame, or dietary sucrose, on children's behavior or cognitive function.(17)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Measures should be taken to minimize the potential for dust explosion. Eye protection is recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral powder for reconstitution, buccal patch, granules, film-coated, and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Alitame.

18 Comments

The intensity of sweeteners relative to sucrose depends upon their concentration, temperature of tasting, and pH, and on the flavor and texture of the product concerned.

Intense sweetening agents will not replace the bulk, textural, or preservative characteristics of sugar, if sugar is removed from a formulation.

Synergistic effects for combinations of sweeteners have been reported, e.g., aspartame with acesulfame potassium.

Aspartame can cause browning when used at high temperatures.

A specification for aspartame is contained in the Food Chemicals Codex (FCC).

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17 Wolraich ML, Lindgreen SD, Stumbo PJ, *et al*. Effects of diets high in sucrose or aspartame on the behavior and cognitive performance of children. *N Engl J Med* 1994; **330**: 301–307.

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21 Authors

H Wang.

22 Date of Revision

12 August 2005.

Attapulgite

1 Nonproprietary Names

BP: Attapulgite

2 Synonyms

Actapulgite; *Attaclay*; *Attacote*; *Attagel*; attapulgus; palygorscite; palygorskite; *Pharmsorb Regular.*

3 Chemical Name and CAS Registry Number

Attapulgite [12174-11-7]

4 Empirical Formula and Molecular Weight

Attapulgite is a purified native hydrated magnesium aluminum silicate consisting of the clay mineral palygorskite, with the empirical formula $Mg(Al_{0.5-1}Fe_{0-0.5})Si_4O_{10}(OH)\cdot 4H_2O$.

5 Structural Formula

See Section 4.

6 Functional Category

Adsorbent.

7 Applications in Pharmaceutical Formulation or Technology

Attapulgite is widely used as an adsorbent in solid dosage forms. Colloidal clays (such as attapulgite) absorb considerable amounts of water to form gels and in concentrations of 2–5% w/v usually form oil-in-water emulsions. Activated attapulgite, which is attapulgite that has been carefully heated to increase its absorptive capacity, is used therapeutically as an adjunct in the management of diarrhea.

8 Description

Attapulgite occurs as a light cream colored, very fine powder. Particle size ranges depend on the grade and manufacturer.

9 Pharmacopeial Specifications

See Table I. *See also* Section 17.

10 Typical Properties

Acidity/alkalinity: pH = 9.5 (5% w/v aqueous suspension)
Angle of repose: 37.2–45.2°(1)
Density: 2.2 g/cm^3
Density (tapped): 0.33 g/cm^3(1)
Flowability: 20.9–29.6% (Carr compressibility index)(1)
Particle size distribution:
<2 μm in size for powder;
2–5 μm in size for aggregate.(1)

Table I: Pharmacopeial specifications for attapulgite.

Test	BP 2004
Identification	+
Characters	+
Acidity or alkalinity (5% w/v aqueous suspension)	7.0–9.5
Adsorptive capacity	5–14%
Arsenic	⩽8 ppm
Heavy metals	⩽20 ppm
Acid-insoluble matter	⩽12.5%
Water-soluble matter	⩽0.5%
Loss on drying	⩽17.0%
Loss on ignition	15.0–27.0%

11 Stability and Storage Conditions

Attapulgite can adsorb water. It should be stored in an airtight container in a cool, dry, location.

12 Incompatibilities

Attapulgite may decrease the bioavailability of some drugs such as loperamide(2) and riboflavin.(3) Oxidation of hydrocortisone is increased in the presence of attapulgite.(4)

13 Method of Manufacture

Attapulgite occurs naturally as the mineral palygorskite.

14 Safety

Attapulgite is widely used in pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material. It is not absorbed following oral administration. In oral preparations, activated attapulgite up to 9 g is used in daily divided doses as an adjunct in the management of diarrhea.(5)

LD_{50} (rat, IP): 0.34 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended. Attapulgite should be handled in a well-ventilated environment and dust generation should be minimized. When heated to decomposition, attapulgite emits acrid smoke and irritating fumes.

16 Regulatory Status

Included in nonparenteral medicines licensed in a number of countries worldwide including the UK and US.

17 Related Substances

Activated attapulgite; magnesium aluminum silicate.

Activated attapulgite

Comments: activated attapulgite is a processed native magnesium aluminum silicate that has been carefully heated to increase its adsorptive capacity. Monographs for activated attapulgite are included in the BP 2004, USP 28, and other pharmacopeias. The USP 28 also includes a monograph for colloidal activated attapulgite.

18 Comments

The EINECS number for attapulgite is 302-243-0.

19 Specific References

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2 Mboya SA, Bhargava HN. Adsorption and desorption of loperamide hydrochloride by activated attapulgites. *Am J Health Syst Pharm* 1995; **52**: 2816–2818.
3 Khalil SAH, Mortada LM, Shams-Eldeen MA, El-Khawas MM. Effect of attapulgite on the bioavailability of a model low dose drug (riboflavine) in humans. *Drug Dev Ind Pharm* 1987; **13**: 369–382.
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Viseras C, Yebra A, López-Galindo A. Characteristics of pharmaceutical grade phyllosilicate compacts. *Pharm Dev Technol* 2000; **5**(1): 53–58.

21 Authors

A Palmieri.

22 Date of Revision

8 August 2005.

Bentonite

1 Nonproprietary Names

BP: Bentonite
JP: Bentonite
PhEur: Bentonitum
USPNF: Bentonite

2 Synonyms

Albagel; E558; *Magnabrite*; mineral soap; *Polargel*; soap clay; taylorite; *Veegum HS*; wilkinite.

3 Chemical Name and CAS Registry Number

Bentonite [1302-78-9]

4 Empirical Formula and Molecular Weight

$Al_2O_3{\cdot}4SiO_2{\cdot}H_2O$ 359.16

Bentonite is a native colloidal hydrated aluminum silicate consisting mainly of montmorillonite, $Al_2O_3{\cdot}4SiO_2{\cdot}H_2O$; it may also contain calcium, magnesium, and iron. The average chemical analysis is expressed as oxides, *see* Table I, in comparison with magnesium aluminum silicate.

Table I: Average chemical analysis of bentonite expressed as oxides in comparison with magnesium aluminum silicate.

	Bentonite	Magnesium aluminum silicate
Silicon dioxide	59.92%	61.1%
Aluminum oxide	19.78%	9.3%
Magnesium oxide	1.53%	13.7%
Ferric oxide	2.96%	0.9%
Calcium oxide	0.64%	2.7%
Sodium oxide	2.06%	2.9%
Potassium oxide	0.57%	0.3%

5 Structural Formula

The PhEur 2005 describes bentonite as a natural clay containing a high proportion of montmorillonite, a native hydrated aluminum silicate in which some aluminum and silicon atoms may be replaced by other atoms such as magnesium and iron.

The USPNF 23 describes bentonite, purified benonite, and bentonite magma in three separate monographs. Bentonite is described as a native, colloidal, hydrated aluminum silicate; and purified bentonite is described as a colloidal montmorillonite that has been processed to remove grit and nonswellable ore compounds.

See also Section 4.

6 Functional Category

Adsorbent; stabilizing agent; suspending agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Bentonite is a naturally occurring hydrated aluminum silicate used primarily in the formulation of suspensions, gels, and sols, for topical pharmaceutical applications. It is also used to suspend powders in aqueous preparations and to prepare cream bases containing oil-in-water emulsifying agents.

Bentonite may also be used in oral pharmaceutical preparations, cosmetics, and food products, *see* Section 18. In oral preparations, bentonite, and other similar silicate clays, can be used to adsorb cationic drugs and so retard their release.(1–3) Adsorbents are also used to mask the taste of certain drugs. *See* Table II.

Bentonite has been investigated as a diagnostic agent for magnetic resonance imaging.(4)

Therapeutically, bentonite has been investigated as an adsorbent for lithium poisoning.(5)

8 Description

Bentonite is a crystalline, claylike mineral, and is available as an odorless, pale buff, or cream to grayish-colored fine powder, which is free from grit. It consists of particles about 50–150 μm in size along with numerous particles about 1–2 μm. Microscopic examination of samples stained with alcoholic methylene blue solution reveals strongly stained blue particles. Bentonite may have a slight earthy taste.

SEM: 1
Excipient: Bentonite
Manufacturer: American Colloid Co.
Lot No.: NMD 11780
Magnification: 600×
Voltage: 10 kV

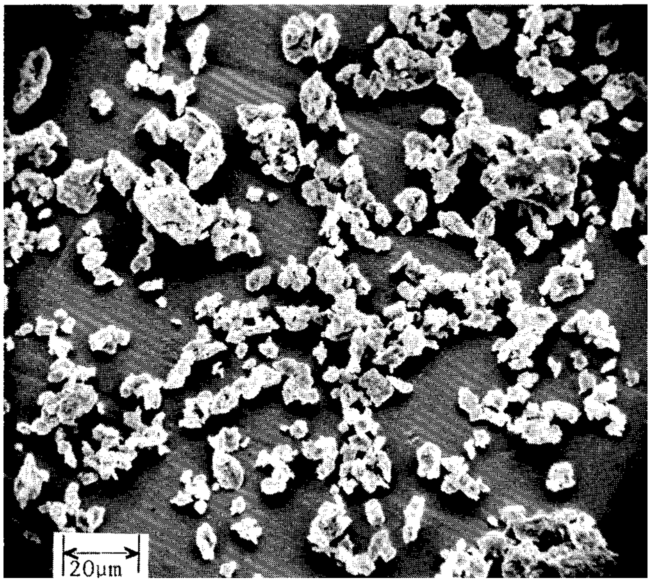
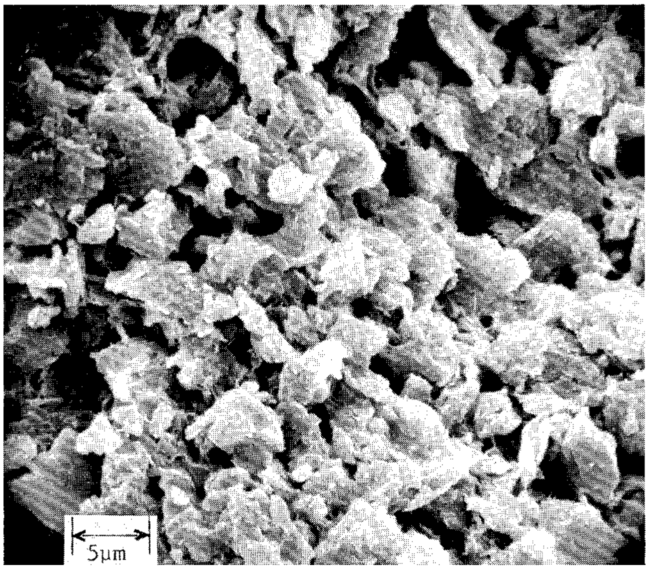


Table II: Uses of bentonite.

Use	Concentration (%)
Adsorbent (clarifying agent)	1.0–2.0
Emulsion stabilizer	1.0
Suspending agent	0.5–5.0

SEM: 2
Excipient: Bentonite
Manufacturer: American Colloid Co.
Lot No: NMD 11780
Magnification: 2400×
Voltage: 20 kV



9 Pharmacopeial Specifications

See Table III.

Table III: Pharmacopeial specifications for bentonite.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	+	+	—
Alkalinity	—	+	—
Microbial limit	—	⩽10^3/g	+
Coarse particles	—	⩽0.5%	—
pH (2% w/v suspension)	9.0–10.5	—	9.5–10.5
Loss on drying	5.0–10.0%	⩽15%	5.0–8.0%
Arsenic	⩽2 ppm	—	⩽5 ppm
Lead	—	—	⩽0.004%
Heavy metals	⩽50 ppm	⩽50 ppm	—
Organic volatile impurities	—	—	+
Gel formation	+	—	+
Sedimentation volume	—	⩽2 mL	—
Swelling power	⩾20 mL	⩾22 mL	⩾24 mL
Fineness of powder	+	—	+

The USPNF 23 also contains specifications for bentonite magma and purified bentonite. *See* Section 17.

10 Typical Properties

Acidity/alkalinity: pH = 9.5–10.5 for a 2% w/v aqueous suspension.

Flowability: no flow.

Hygroscopicity: bentonite is hygroscopic.(6) *See also* Figure 1.

Moisture content: 5–12%.

Solubility: practically insoluble in ethanol, fixed oils, glycerin, propan-2-ol, and water. Bentonite swells to about 12 times its original volume in water, to form viscous homogeneous suspensions, sols, or gels depending upon the concentration. Bentonite does not swell in organic solvents. Sols and gels may be conveniently prepared by sprinkling the bentonite on the surface of hot water and allowing to stand for 24 hours, stirring occasionally when the bentonite has become thoroughly wetted. Water should not be added to bentonite alone, but bentonite may be satisfactorily dispersed in water if it is first triturated with glycerin or mixed with a powder such as zinc oxide. A 7% w/v aqueous suspension of bentonite is just pourable. *See also* Section 12.

Viscosity (dynamic): 75–225 mPa s (75–225 cP) for a 5.5% w/v aqueous suspension at 25°C. Viscosity increases with increasing concentration.

11 Stability and Storage Conditions

Bentonite is hygroscopic, and sorption of atmospheric water should be avoided.

Aqueous bentonite suspensions may be sterilized by autoclaving. The solid material may be sterilized by maintaining it at 170°C for 1 hour after drying at 100°C.

Bentonite should be stored in an airtight container in a cool, dry place.

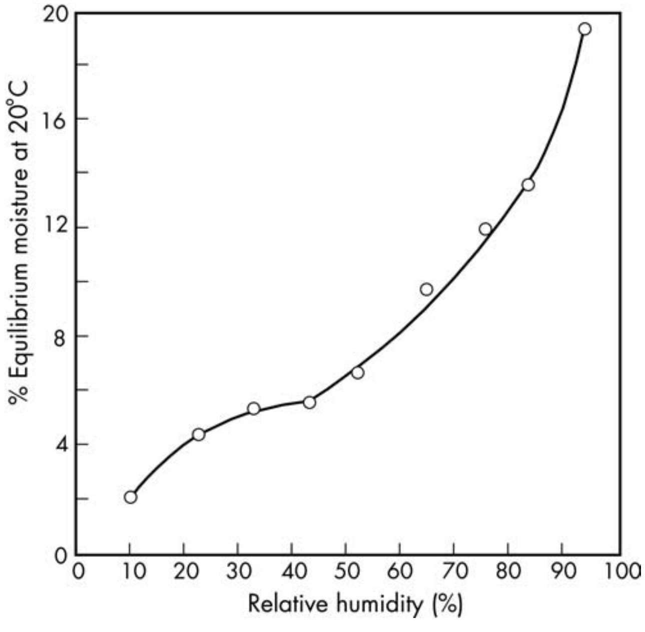


Figure 1: Equilibrium, moisture content of bentonite USPNF.

12 Incompatibilities

Aqueous bentonite suspensions retain their viscosity above pH 6, but are precipitated by acids. Acid-washed bentonite does not have suspending properties. The addition of alkaline materials, such as magnesium oxide, increases gel formation.

Addition of significant amounts of alcohol to aqueous preparations will precipitate bentonite, primarily by dehydration of the lattice structure; *see also* Section 18.

Bentonite particles are negatively charged and flocculation occurs when electrolytes or positively charged suspensions are added. Bentonite is thus said to be incompatible with strong electrolytes, although this effect is sometimes used beneficially to clarify turbid liquids.

The antimicrobial efficacy of cationic preservatives may be reduced in aqueous bentonite suspensions, but nonionic and anionic preservatives are unaffected.(7)

Bentonite is incompatible with acriflavine hydrochloride.

13 Method of Manufacture

Bentonite is a native, colloidal, hydrated aluminum silicate, found in regions of Canada and the USA. The mined ore is processed to remove grit and nonswelling materials so that it is suitable for pharmaceutical applications.

14 Safety

Bentonite is mainly used in topical pharmaceutical formulations but has also been used in oral pharmaceutical preparations, food products, and cosmetics.

Following oral administration, bentonite is not absorbed from the gastrointestinal tract. Bentonite is generally regarded as a nontoxic and nonirritant material.

LD_{50} (rat, IV): 0.035 g/kg(8)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended. Bentonite should be handled in a well-ventilated environment and dust generation minimized.

16 Regulatory Status

Accepted in Europe as a food additive in certain applications. Included in the FDA Inactive Ingredients Guide (oral capsules, tablets and suspensions, topical suspensions, controlled release transdermal films and vaginal suppositories). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Bentonite magma; kaolin; magnesium aluminum silicate; magnesium trisilicate; purified bentonite; talc.

Bentonite magma

Comments: a 5% w/w suspension of bentonite in purified water appears in some pharmacopeias, such as the USPNF 23.

Purified bentonite

Acidity/alkalinity: pH = 9.0–10.0 for a 5% w/w aqueous suspension.

Viscosity (dynamic): 40–200 mPa s (40–200 cP) for a 5% w/w aqueous suspension.

Comments: specifications for purified bentonite occur in some pharmacopeias such as the USPNF 23. Purified bentonite is bentonite that has been processed to remove grit and nonswellable ore components.

18 Comments

Bentonite may be used with concentrations of up to 30% ethanol or propan-2-ol; 50% glycerin; 30% propylene glycol; or high molecular weight polyethylene glycols. The EINECS number for bentonite is 215-108-5.

Bentonite is used in the food industry as a processing aid as a clarifying or filter agent. A specification for bentonite is contained in the Food Chemicals Codex (FCC).

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21 Authors

A Palmieri.

22 Date of Revision

8 August 2005.

Benzalkonium Chloride

1 Nonproprietary Names

BP: Benzalkonium chloride
JP: Benzalkonium chloride
PhEur: Benzalkonii chloridum
USPNF: Benzalkonium chloride

2 Synonyms

Alkylbenzyldimethylammonium chloride; alkyl dimethyl benzyl ammonium chloride; BKC; *Hyamine 3500*; *Pentonium*; *Zephiran*.

3 Chemical Name and CAS Registry Number

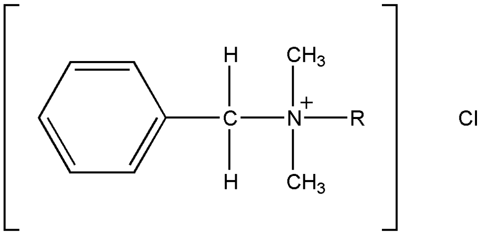
Alkyldimethyl(phenylmethyl)ammonium chloride [8001-54-5]

4 Empirical Formula and Molecular Weight

The USPNF 23 describes benzalkonium chloride as a mixture of alkylbenzyldimethylammonium chlorides of the general formula $[C_6H_5CH_2N(CH_3)_2R]Cl$, where R represents a mixture of alkyls, including all or some of the group beginning with n-C_8H_{17} and extending through higher homologs, with n-$C_{12}H_{25}$, n-$C_{14}H_{29}$, and n-$C_{16}H_{33}$ comprising the major portion.

The average molecular weight of benzalkonium chloride is 360.

5 Structural Formula



R = mixture of alkyls: n-C_8H_{17} to n-$C_{18}H_{37}$; mainly n-$C_{12}H_{25}$ (dodecyl), n-$C_{14}H_{29}$ (tetradecyl), and n-$C_{16}H_{33}$ (hexadecyl).

6 Functional Category

Antimicrobial preservative; antiseptic; disinfectant; solubilizing agent; wetting agent.

7 Applications in Pharmaceutical Formulation or Technology

Benzalkonium chloride is a quaternary ammonium compound used in pharmaceutical formulations as an antimicrobial preservative in applications similar to other cationic surfactants, such as cetrimide.

In ophthalmic preparations, benzalkonium chloride is one of the most widely used preservatives,(1) at a concentration of 0.01–0.02% w/v. Often it is used in combination with other preservatives or excipients, particularly 0.1% w/v disodium edetate, to enhance its antimicrobial activity against strains of *Pseudomonas*.

In nasal,(2) and otic formulations a concentration of 0.002–0.02% w/v is used, sometimes in combination with 0.002–0.005% w/v thimerosal. Benzalkonium chloride 0.01% w/v is also employed as a preservative in small-volume parenteral products. Benzalkonium chloride was also shown to enhance the topical penetration of lorazepam.(3)

Benzalkonium chloride is additionally used as a preservative in cosmetics.

8 Description

Benzalkonium chloride occurs as a white or yellowish-white amorphous powder, a thick gel, or gelatinous flakes. It is hygroscopic, soapy to the touch, and has a mild aromatic odor and very bitter taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for benzalkonium chloride.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	+	+	—
Acidity or alkalinity	—	+	—
Appearance of solution	+	+	—
Water	$\leqslant$15.0%	$\leqslant$10.0%	$\leqslant$15.0%
Residue on ignition	$\leqslant$0.2%	—	$\leqslant$2.0%
Sulfated ash	—	$\leqslant$0.1%	—
Water-insoluble matter	—	—	+
Foreign amines	—	+	+
Ratio of alkyl components	—	—	+
Petroleum ether-soluble substances	$\leqslant$1.0%	—	—
Assay (dried basis)			
of n-$C_{12}H_{25}$	—	—	$\geqslant$40.0%
of n-$C_{14}H_{29}$	—	—	$\geqslant$20.0%
of n-$C_{12}H_{25}$ and n-$C_{14}H_{29}$	—	—	$\geqslant$70.0%
for total alkyl content	95.0–105.0%	95.0–104.0%	97.0–103.0%

10 Typical Properties

Acidity/alkalinity: pH = 5–8 for a 10% w/v aqueous solution.

Antimicrobial activity: benzalkonium chloride solutions are active against a wide range of bacteria, yeasts, and fungi. Activity is more marked against Gram-positive than Gram-negative bacteria and minimal against bacterial endospores and acid-fast bacteria, *see* Table II. The antimicrobial activity of benzalkonium chloride is significantly dependent upon the alkyl composition of the homolog mixture.(4) Benzalkonium chloride is ineffective against some *Pseudomonas aeruginosa* strains, *Mycobacterium tuberculosis*, *Trichophyton interdigitale*, and *T. rubrum*. However, combined with disodium edetate (0.01–0.1% w/v), benzyl alcohol, phenylethanol, or phenylpropanol, the activity against *Pseudomonas aeruginosa* is increased.(5) Antimicrobial activity may also be enhanced by the addition of phenylmercuric acetate, phenylmercuric borate, chlorhexidine, cetrimide, or *m*-cresol.(6,7) In the presence of citrate and phosphate buffers (but not borate), activity against *Pseudomonas* can be reduced. *See also* Sections 11 and 12. Benzalkonium chloride is relatively inactive against spores and molds, but is active against some viruses, including HIV.(8) Inhibitory activity increases with pH, although antimicrobial activity occurs at pH 4–10.

Table II: Minimum inhibitory concentrations (MICs) of benzalkonium chloride.

Microorganism	MIC (μg/mL)
Aerobacter aerogenes	64
Clostridium histolyticum	5
Clostridium oedematiens	5
Clostridium tetani	5
Clostridium welchii	5
Escherichia coli	16
Pneumococcus II	5
Proteus vulgaris	64
Pseudomonas aeruginosa	30
Salmonella enteritidis	30
Salmonella paratyphi	16
Salmonella typhosa	4
Shigella dysenteriae	2
Staphylococcus aureus	1.25
Streptococcus pyrogenes	1.25
Vibrio cholerae	2

Density: ≈0.98 g/cm^3 at 20°C

Melting point: ≈40°C

Partition coefficients: the octanol : water partition coefficient varies with the alkyl chain length of the homolog; 9.98 for C_{12}, 32.9 for C_{14}, and 82.5 for C_{16}.

Solubility: practically insoluble in ether; very soluble in acetone, ethanol (95%), methanol, propanol, and water. Aqueous solutions of benzalkonium chloride foam when shaken, have a low surface tension and possess detergent and emulsifying properties.

11 Stability and Storage Conditions

Benzalkonium chloride is hygroscopic and may be affected by light, air, and metals.

Solutions are stable over a wide pH and temperature range and may be sterilized by autoclaving without loss of effectiveness. Solutions may be stored for prolonged periods at room temperature. Dilute solutions stored in polyvinyl chloride or polyurethane foam containers may lose antimicrobial activity.

The bulk material should be stored in an airtight container, protected from light and contact with metals, in a cool, dry place.

12 Incompatibilities

Incompatible with aluminum, anionic surfactants, citrates, cotton, fluorescein, hydrogen peroxide, hypromellose,(9) iodides, kaolin, lanolin, nitrates, nonionic surfactants in high concentration, permanganates, protein, salicylates, silver salts, soaps, sulfonamides, tartrates, zinc oxide, zinc sulfate, some rubber mixes, and some plastic mixes.

Benzalkonium chloride has been shown to be adsorbed to various filtering membranes, especially those that are hydrophobic or anionic.(10)

13 Method of Manufacture

Benzalkonium chloride is formed by the reaction of a solution of *N*-alkyl-*N*-methylbenzamine with methyl chloride in an organic solvent suitable for precipitating the quaternary compound as it is formed.

14 Safety

Benzalkonium chloride is usually nonirritating, nonsensitizing, and is well tolerated in the dilutions normally employed on the skin and mucous membranes. However, benzalkonium chloride has been associated with adverse effects when used in some pharmaceutical formulations.(11)

Ototoxicity can occur when benzalkonium chloride is applied to the ear(12) and prolonged contact with the skin can occasionally cause irritation and hypersensitivity. Benzalkonium chloride is also known to cause bronchoconstriction in some asthmatics when used in nebulizer solutions.(13–17)

Toxicity experiments with rabbits have shown benzalkonium chloride to be harmful to the eye in concentrations higher than that normally used as a preservative. However, the human eye appears to be less affected than the rabbit eye and many ophthalmic products have been formulated with benzalkonium chloride 0.01% w/v as the preservative.

Benzalkonium chloride is not suitable for use as a preservative in solutions used for storing and washing hydrophilic soft contact lenses, as the benzalkonium chloride can bind to the lenses and may later produce ocular toxicity when the lenses are worn.(18) Solutions stronger than 0.03% w/v concentration entering the eye require prompt medical attention.

Local irritation of the throat, esophagus, stomach, and intestine can occur following contact with strong solutions (>0.1% w/v). The fatal oral dose of benzalkonium chloride in humans is estimated to be 1–3 g. Adverse effects following oral ingestion include vomiting, collapse, and coma. Toxic doses lead to paralysis of the respiratory muscles, dyspnea, and cyanosis.

LD_{50} (mouse, oral): 150 mg/kg(19)
LD_{50} (rat, IP): 14.5 mg/kg
LD_{50} (rat, IV): 13.9 mg/kg
LD_{50} (rat, oral): 300 mg/kg
LD_{50} (rat, skin): 1.42 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Benzalkonium chloride is irritant to the skin and eyes and repeated exposure to the skin may cause hypersensitivity. Concentrated benzalkonium chloride solutions accidentally spilled on the skin may produce corrosive skin lesions with deep necrosis and scarring, and should be washed immediately with water, followed by soap solutions applied freely. Gloves, eye protection, and suitable protective clothing should be worn.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (inhalations, IM injections, nasal, ophthalmic, otic, and topical preparations). Included in nonparenteral medicines licensed in the UK. It is also included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Benzethonium chloride; cetrimide.

18 Comments

Benzalkonium chloride has been used in antiseptic wipes and has been shown to produce significantly less stinging or burning than isopropyl alcohol and hydrogen peroxide.(20) The EINECS numbers for benzalkonium chloride are 264-151-6; 260-080-8; 269-919-4; 270-325-2; 287-089-1.

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21 Authors

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22 Date of Revision

12 August 2005.

Benzethonium Chloride

1 Nonproprietary Names

BP: Benzethonium chloride
JP: Benzethonium chloride
PhEur: Benzethonii chloridum
USP: Benzethonium chloride

2 Synonyms

Benzyldimethyl-[2-[2-(*p*-1,1,3,3-tetramethylbutylphenoxy) ethoxy]ethyl]ammonium chloride; BZT; diisobutylphenoxy-ethoxyethyl dimethyl benzyl ammonium chloride; *Hyamine 1622*.

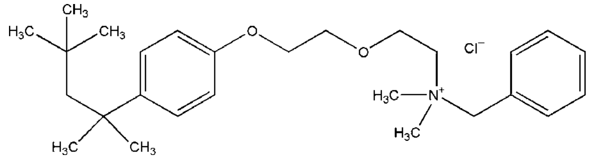
3 Chemical Name and CAS Registry Number

N,*N*-Dimethyl-*N*-[2-[2-[4-(1,1,3,3-tetramethylbutyl)phenoxy] ethoxy]ethyl]benzene-methanaminium chloride [121-54-0]

4 Empirical Formula and Molecular Weight

$C_{27}H_{42}ClNO_2$ 448.10

5 Structural Formula



6 Functional Category

Antimicrobial preservative; antiseptic; disinfectant.

7 Applications in Pharmaceutical Formulation or Technology

Benzethonium chloride is a quaternary ammonium compound used in pharmaceutical formulations as an antimicrobial preservative. Typically, it is used for this purpose in injections, ophthalmic and otic preparations at concentrations 0.01–0.02% w/v. Benzethonium chloride may also be used as a wetting and solubilizing agent, and as a topical disinfectant.

In cosmetics such as deodorants, benzethonium chloride may be used as an antimicrobial preservative in concentrations up to 0.5% w/v.

The physical properties and applications of benzethonium chloride are similar to those of other cationic surfactants such as cetrimide.

8 Description

Benzethonium chloride occurs as a white crystalline material with a mild odor and very bitter taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for benzethonium chloride.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	—	+	—
Appearance of solution	—	+	—
Acidity or alkalinity	—	+	—
Melting range	158–164°C	158–164°C	158–163°C
Loss on drying	≤5.0%	≤5.0%	≤5.0%
Residue on ignition	≤0.1%	—	≤0.1%
Sulfated ash	—	≤0.1%	—
Ammonium compounds	+	≤50 ppm	+
Assay (dried basis)	≥97.0%	97.0–103.0%	97.0–103.0%

10 Typical Properties

Acidity/alkalinity: pH = 4.8–5.5 for a 1% w/v aqueous solution.

Antimicrobial activity: optimum antimicrobial activity occurs between pH 4–10. Preservative efficacy is enhanced by ethanol and reduced by soaps and other anionic surfactants. For typical minimum inhibitory concentrations (MICs) *see* Table II.$^{(1)}$

Table II: Minimum inhibitory concentration (MIC) for benzethonium chloride.

Microorganism	MIC (μg/mL)
Aspergillus niger	128
Candida albicans	64
Escherichia coli	32
Penicillium notatum	64
Proteus vulgaris	64
Pseudomonas aeruginosa	250
Pseudomonas cepacia	250
Pseudomonas fluorescens	250
Staphylococcus aureus	0.5
Streptococcus pyogenes	0.5

Solubility: soluble 1 in less than 1 of acetone, chloroform, ethanol (95%), and water; soluble 1 in 6000 of ether. Dissolves in water to produce a foamy, soapy solution.

11 Stability and Storage Conditions

Benzethonium chloride is stable. Aqueous solutions may be sterilized by autoclaving.

The bulk material should be stored in an airtight container protected from light, in a cool, dry place.

12 Incompatibilities

Benzethonium chloride is incompatible with soaps and other anionic surfactants and may be precipitated from solutions greater than 2% w/v concentration by the addition of mineral acids and some salt solutions.

13 Method of Manufacture

p-Diisobutylphenol is condensed in the presence of a basic catalyst with β,β′-dichlorodiethyl ether to yield 2-[2-[4-(1,1,3,3-tetramethylbutyl)phenoxy]ethoxy]ethyl chloride. Alkaline dimethylamination then produces the corresponding tertiary amine which, after purification by distillation, is dissolved in a suitable organic solvent and treated with benzyl chloride to precipitate benzethonium chloride.(2)

14 Safety

Benzethonium chloride is readily absorbed and is generally regarded as a toxic substance when administered orally. Ingestion may cause vomiting, collapse, convulsions, and coma. The probable lethal human oral dose is estimated to be 50–500 mg/kg body-weight.

The topical use of solutions containing greater than 5% w/v benzethonium chloride can cause irritation although benzethonium chloride is not regarded as a sensitizer. The use of 0.5% w/v benzethonium chloride in cosmetics is associated with few adverse effects. A maximum concentration of 0.02% w/v benzethonium chloride is recommended for use in cosmetics used in the eye area and this is also the maximum concentration generally used in pharmaceutical formulations such as injections and ophthalmic preparations.(3)

See also Benzalkonium Chloride.

LD_{50} (mouse, IP): 15.5 mg/kg(4)
LD_{50} (mouse, IV): 30 mg/kg
LD_{50} (mouse, oral): 338 mg/kg
LD_{50} (rat, IP): 16.5 mg/kg
LD_{50} (rat, IV): 19 mg/kg
LD_{50} (rat, oral): 368 mg/kg
LD_{50} (rat, SC): 119 mg/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IM and IV injections, ophthalmic and otic preparations). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Benzalkonium chloride; cetrimide.

18 Comments

Benzethonium chloride has been used therapeutically as a disinfectant and topical anti-infective agent. However, its use in these applications has largely been superseded by other more effective antimicrobials and it is now largely used solely as a preservative in a limited number of pharmaceutical and cosmetic formulations.

The EINECS number for benzethonium chloride is 204-479-9.

19 Specific References

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20 General References

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21 Authors

LME McIndoe.

22 Date of Revision

12 August 2005.

Benzoic Acid

1 Nonproprietary Names

BP: Benzoic acid
JP: Benzoic acid
PhEur: Acidum benzoicum
USP: Benzoic acid

2 Synonyms

Benzenecarboxylic acid; benzeneformic acid; carboxybenzene; dracylic acid; E210; phenylcarboxylic acid; phenylformic acid.

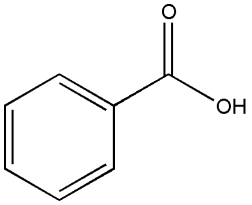
3 Chemical Name and CAS Registry Number

Benzoic acid [65-85-0]

4 Empirical Formula and Molecular Weight

$C_7H_6O_2$ 122.12

5 Structural Formula



6 Functional Category

Antimicrobial preservative; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Benzoic acid is widely used in cosmetics, foods, and pharmaceuticals (*see* Table I), as an antimicrobial preservative.(1–3) Greatest activity is seen at pH values between 2.5–4.5; *see* Section 10.

Benzoic acid also has a long history of use as an antifungal agent(4) in topical therapeutic preparations such as Whitfield's ointment (benzoic acid 6% and salicylic acid 3%).

Table I: Uses of benzoic acid.

Use	Concentration (%)
IM and IV injections	0.17
Oral solutions	0.01–0.1
Oral suspensions	0.1
Oral syrups	0.15
Topical preparations	0.1–0.2
Vaginal preparations	0.1–0.2

8 Description

Benzoic acid occurs as feathery, light, white or colorless crystals or powder. It is essentially tasteless and odorless or with a slight characteristic odor suggestive of benzoin.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for benzoic acid.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	—	+	—
Congealing range	121–124°C	121–124°C	121–123°C
Water	⩽0.5%	—	⩽0.7%
Residue on ignition	⩽0.05%	⩽0.1%	⩽0.05%
Readily carbonizable substances	+	+	+
Readily oxidizable substances	+	+	+
Heavy metals	⩽20 ppm	⩽10 ppm	⩽10 ppm
Halogenated compounds and halides	+	⩽300 ppm	—
Appearance of solution	—	+	—
Assay	⩾99.5%	99.0–100.5%	99.5–100.5%

10 Typical Properties

Acidity/alkalinity: pH = 2.8 (saturated aqueous solution at 25°C)

Antimicrobial activity: only the undissociated acid shows antimicrobial properties, the activity therefore depends on the pH of the medium. Optimum activity occurs at pH values below 4.5; at values above pH 5, benzoic acid is almost inactive.(5) It has been reported that antimicrobial activity is enhanced by the addition of protamine, a basic protein.(6)

Bacteria: moderate bacteriostatic activity against most species of Gram-positive bacteria. Typical MIC is 100 μg/mL. Activity is less, in general, against Gram-negative bacteria. MIC for Gram-negative bacteria may be up to 1600 μg/mL.

Molds: moderate activity. Typical MICs are 400–1000 μg/mL at pH 3; 1000–2000 μg/mL at pH 5.

Spores: inactive against spores.

Yeasts: moderate activity. Typical MIC is 1200 μg/mL. The addition of propylene glycol may enhance the fungistatic activity of benzoic acid.

Autoignition temperature: 570°C

Boiling point: 249.2°C

Density:

1.311 g/cm^3 for solid at 24°C;
1.075 g/cm^3 for liquid at 130°C.

Dissociation constant: the dissociation of benzoic acid in mixed solvents is dictated by specific solute–solvent interactions as

well as by relative solvent basicity. Increasing the organic solvent fraction favors the free acid form.(7)
$pK_a = 4.19$ at 25°C;
$pK_a = 5.54$ in methanol 60%.

Flash point: 121–131°C

Melting point: 122°C (begins to sublime at 100°C).

Moisture content: 0.17–0.42% w/w

Partition coefficients:
Benzene : water = 0.0044;(8)
Cyclohexane : water = 0.30;(9)
Octanol : water = 1.87.(10)

Refractive index:
$n_D^{15} = 1.5397$ for solid;
$n_D^{132} = 1.504$ for liquid.

Solubility: apparent aqueous solubility of benzoic acid may be enhanced by the addition of citric acid or sodium acetate to the solution; *see* Table III.

Table III: Solubility of benzoic acid.

Solvent	Solubility at 25°C unless otherwise stated
Acetone	1 in 2.3
Benzene	1 in 9.4
Carbon disulfide	1 in 30
Carbon tetrachloride	1 in 15.2
Chloroform	1 in 4.5
Cyclohexane	1 in 14.6(9)
Ethanol	1 in 2.7 at 15°C 1 in 2.2
Ethanol (76%)	1 in 3.72(11)
Ethanol (54%)	1 in 6.27(11)
Ethanol (25%)	1 in 68(11)
Ether	1 in 3
Fixed oils	Freely soluble
Methanol	1 in 1.8
Toluene	1 in 11
Water	1 in 300

11 Stability and Storage Conditions

Aqueous solutions of benzoic acid may be sterilized by autoclaving or by filtration.

A 0.1% w/v aqueous solution of benzoic acid has been reported to be stable for at least 8 weeks when stored in polyvinyl chloride bottles, at room temperature.(12)

When added to a suspension, benzoic acid dissociates, with the benzoate anion adsorbing onto the suspended drug particles. This adsorption alters the charge at the surface of the particles, which may in turn affect the physical stability of the suspension.(13)

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Undergoes typical reactions of an organic acid, e.g. with alkalis or heavy metals. Preservative activity may be reduced by interaction with kaolin.(14)

13 Method of Manufacture

Although benzoic acid occurs naturally, it is produced commercially by several synthetic methods. One process involves the continuous liquid-phase oxidation of toluene in the presence of a cobalt catalyst at 150–200°C and 0.5–5.0 MPa (5.0–50.0 atm) pressure to give a yield of approximately 90% benzoic acid.

Benzoic acid can also be produced commercially from benzotrichloride or phthalic anhydride. Benzotrichloride, produced by chlorination of toluene, is reacted with 1 mole of benzoic acid to yield 2 moles of benzoyl chloride. The benzoyl chloride is then converted to 2 moles of benzoic acid by hydrolysis. Yield is 75–80%.

In another commercial process, phthalic anhydride is converted to benzoic acid, in about an 85% yield, by hydrolysis in the presence of heat and chromium and disodium phthalates.

Crude benzoic acid is purified by sublimation or recrystallization.

14 Safety

Ingested benzoic acid is conjugated with glycine in the liver to yield hippuric acid, which is then excreted in the urine;(15) care should be taken when administering benzoic acid to patients with chronic liver disease.(16) Benzoic acid is a gastric irritant, and a mild irritant to the skin.(17–19) It is also a mild irritant to the eyes and mucous membranes.(20) Allergic reactions to benzoic acid have been reported, although a controlled study indicated that the incidence of urticaria in patients given benzoic acid is no greater than in those given a lactose placebo.(21)

The WHO acceptable daily intake of benzoic acid and other benzoates, calculated as benzoic acid, has been set at up to 5 mg/kg body-weight.(22,23) The minimum lethal human oral dose of benzoic acid is 500 mg/kg body-weight.(24)

LD_{50} (cat, oral): 2 g/kg(24)
LD_{50} (dog, oral): 2 g/kg
LD_{50} (mouse, IP): 1.46 g/kg
LD_{50} (mouse, oral): 1.94 g/kg
LD_{50} (rat, oral): 1.7 g/kg

See also Sodium benzoate.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Benzoic acid may be harmful by inhalation, ingestion, or skin absorption and may be irritant to the eyes, skin, and mucous membranes. Benzoic acid should be handled in a well-ventilated environment; eye protection, gloves, and a dust mask or respirator are recommended. Benzoic acid is flammable.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IM and IV injections, irrigation solutions, oral solutions, suspensions, syrups and tablets, rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Potassium benzoate; sodium benzoate.

18 Comments

Benzoic acid is known to dimerize in many nonpolar solvents. This property, coupled with pH-dependent dissociation in aqueous media, comprises a classic textbook example of the effects of dissociation and molecular association on apparent partitioning behavior. The principles involved may be practically applied in determination of the total concentration of benzoate necessary to provide a bacteriostatic level of benzoic acid in the aqueous phase of an oil-in-water emulsion.

A specification for benzoic acid is contained in the Food Chemicals Codex (FCC).

The EINECS number for benzoic acid is 200-618-2.

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21 Authors

PJ Weller.

22 Date of Revision

14 August 2005.

Benzyl Alcohol

1 Nonproprietary Names

BP: Benzyl alcohol
JP: Benzyl alcohol
PhEur: Alcohol benzylicus
USPNF: Benzyl alcohol

2 Synonyms

Benzenemethanol; α-hydroxytoluene; phenylcarbinol; phenylmethanol; α-toluenol.

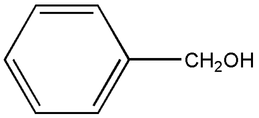
3 Chemical Name and CAS Registry Number

Benzenemethanol [100-51-6]

4 Empirical Formula and Molecular Weight

C_7H_8O 108.14

5 Structural Formula



6 Functional Category

Antimicrobial preservative; disinfectant; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Benzyl alcohol is an antimicrobial preservative used in cosmetics, foods, and a wide range of pharmaceutical formulations,(1–4) including oral and parenteral preparations, at concentrations up to 2.0% v/v. In cosmetics, concentrations up to 3.0% v/v may be used as a preservative. Concentrations of 5% v/v or more are employed as a solubilizer, while a 10% v/v solution is used as a disinfectant.

Benzyl alcohol 10% v/v solutions also have some local anesthetic properties, which are exploited in some parenterals, cough products, ophthalmic solutions, ointments, and dermatological aerosol sprays.

Although widely used as an antimicrobial preservative, benzyl alcohol has been associated with some fatal adverse reactions when administered to neonates. It is now recommended that parenteral products preserved with benzyl alcohol, or other antimicrobial preservatives, should not be used in newborn infants if at all possible; *see* Section 14.

8 Description

A clear, colorless, oily liquid with a faint aromatic odor and a sharp, burning taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for benzyl alcohol.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	+	+	—
Solubility	—	+	—
Acidity	+	+	+
Clarity of solution	+	+	—
Specific gravity	1.043–1.053	1.043–1.049	1.042–1.047
Distilling range	202.5–206.5°C	—	—
Refractive index	1.538–1.541	1.538–1.541	1.539–1.541
Residue on ignition	⩽0.005%	—	⩽0.005%
Nonvolatile matter	—	⩽0.05%	⩽1 mg
Chlorinated compounds	+	—	⩽0.03%
Benzaldehyde	+	+	⩽0.2%
Peroxide value	—	⩽5	—
Organic volatile impurities	—	—	+
Assay	⩾98.0%	98.0–100.5%	97.0–100.5%

10 Typical Properties

Acidity/alkalinity: aqueous solutions are neutral to litmus.

Antimicrobial activity: benzyl alcohol is bacteriostatic and is used as an antimicrobial preservative against Gram-positive bacteria, molds, fungi, and yeasts, although it possesses only modest bactericidal properties. Optimum activity occurs at pH below 5; little activity is shown above pH 8. Antimicrobial activity is reduced in the presence of nonionic surfactants, such as polysorbate 80. However, the reduction in activity is less than is the case with either hydroxybenzoate esters or quaternary ammonium compounds. The activity of benzyl alcohol may also be reduced by incompatibilities with some packaging materials, particularly polyethylene; *see* Section 12.

See Table II for reported minimum inhibitory concentrations (MICs).

Table II: Minimum inhibitory concentrations (MICs) of benzyl alcohol.(4)

Microorganism	MIC (μg/mL)
Aspergillus niger	5000
Candida albicans	2500
Escherichia coli	2000
Pseudomonas aeruginosa	2000
Staphylococcus aureus	25

Bacteria: benzyl alcohol is moderately active against most Gram-positive organisms (typical MICs are 3–5 mg/mL), although some Gram-positive bacteria are very sensitive

(MICs 0.025–0.05 mg/mL). In general, benzyl alcohol is less active against Gram-negative organisms.

Fungi: benzyl alcohol is effective against molds and yeasts; typical MICs are 3–5 mg/mL.

Spores: benzyl alcohol is inactive against spores, but activity may be enhanced by heating. Benzyl alcohol 1% v/v, at pH 5–6, has been claimed to be as effective as phenylmercuric nitrate 0.002% w/v against *Bacillus stearothermophilus* at 100°C for 30 min.

Autoignition temperature: 436.5°C
Boiling point: 204.7°C
Flammability: flammable. Limits in air 1.7–15.0% v/v.
Flash point:
100.6°C (closed cup);
104.5°C (open cup).
Freezing point: −15°C
Partition coefficients:
Liquid paraffin : water = 0.2;
Peanut oil : water = 1.3.
Solubility: *see* Table III.

Table III: Solubility of benzyl alcohol.

Solvent	Solubility at 20°C unless otherwise stated
Chloroform	Miscible in all proportions
Ethanol	Miscible in all proportions
Ethanol (50%)	1 in 2.5
Ether	Miscible in all proportions
Fixed and volatile oils	Miscible in all proportions
Water	1 in 25 at 25°C 1 in 14 at 90°C

Surface tension: 38.8 mN/m (38.8 dynes/cm)
Vapor density (relative): 3.72 (air = 1)
Vapor pressure:
13.3 Pa (0.1 mmHg) at 30°C;
1.769 kPa (13.3 mmHg) at 100°C.
Viscosity (dynamic): 6 mPa s (6 cP) at 20°C

11 Stability and Storage Conditions

Benzyl alcohol oxidizes slowly in air to benzaldehyde and benzoic acid; it does not react with water. Aqueous solutions may be sterilized by filtration or autoclaving; some solutions may generate benzaldehyde during autoclaving.

Benzyl alcohol may be stored in metal or glass containers. Plastic containers should not be used; exceptions to this include polypropylene containers or vessels coated with inert fluorinated polymers such as Teflon; *see* Section 12.

Benzyl alcohol should be stored in an airtight container, protected from light, in a cool, dry place.

12 Incompatibilities

Benzyl alcohol is incompatible with oxidizing agents and strong acids. It can also accelerate the autoxidation of fats.

Although antimicrobial activity is reduced in the presence of nonionic surfactants, such as polysorbate 80, the reduction is less than is the case with hydroxybenzoate esters or quaternary ammonium compounds.

Benzyl alcohol is incompatible with methylcellulose and is only slowly sorbed by closures composed of natural rubber, neoprene, and butyl rubber closures, the resistance of which can be enhanced by coating with fluorinated polymers.(5) However, a 2% v/v aqueous solution in a polyethylene container, stored at 20°C, may lose up to 15% of its benzyl alcohol content in 13 weeks.(6) Losses to polyvinyl chloride and polypropylene containers under similar conditions are usually negligible. Benzyl alcohol can damage polystyrene syringes by extracting some soluble components.(7)

13 Method of Manufacture

Benzyl alcohol is prepared commercially by the distillation of benzyl chloride with potassium or sodium carbonate. It may also be prepared by the Cannizzaro reaction of benzaldehyde and potassium hydroxide.

14 Safety

Benzyl alcohol is used in a wide variety of pharmaceutical formulations. It is metabolized to benzoic acid, which is further metabolized in the liver by conjugation with glycine to form hippuric acid, which is excreted in the urine.

Ingestion or inhalation of benzyl alcohol may cause headache, vertigo, nausea, vomiting, and diarrhea. Overexposure may result in CNS depression and respiratory failure. However, the concentrations of benzyl alcohol normally employed as a preservative are not associated with such adverse effects.

Reports of adverse reactions to benzyl alcohol(8,9) used as an excipient include toxicity following intravenous administration;(10,11) neurotoxicity in patients administered benzyl alcohol in intrathecal preparations;(12) hypersensitivity,(13,14) although relatively rare; and a fatal toxic syndrome in premature infants.(15–17)

The fatal toxic syndrome in low-birth-weight neonates, which includes symptoms of metabolic acidosis and respiratory depression, was attributed to the use of benzyl alcohol as a preservative in solutions used to flush umbilical catheters. As a result of this, the FDA has recommended that benzyl alcohol should not be used in such flushing solutions and has advised against the use of medicines containing preservatives in the newborn.(18,19)

The WHO has set the estimated acceptable daily intake of the benzyl/benzoic moiety at up to 5 mg/kg body-weight daily.(20)

LD_{50} (mouse, IV): 0.32 g/kg(21)
LD_{50} (mouse, oral): 1.36 g/kg
LD_{50} (rat, IP): 0.4 g/kg
LD_{50} (rat, IV): 0.05 g/kg
LD_{50} (rat, oral): 1.23 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Benzyl alcohol (liquid and vapor) is irritant to the skin, eyes, and mucous membranes. Eye protection, gloves, and protective clothing are recommended. Benzyl alcohol should be handled in a well-ventilated environment; a self-contained breathing apparatus is recommended in areas of poor ventilation. Benzyl alcohol is flammable.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (dental injections, oral capsules, solutions and tablets, topical, and vaginal preparations). Included in parenteral and nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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18 Comments

The EINECS number for benzyl alcohol is 202-859-9.

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21 Authors

E Cahill.

22 Date of Revision

15 August 2005.

Benzyl Benzoate

1 Nonproprietary Names

BP: Benzyl benzoate
JP: Benzyl benzoate
PhEur: Benzylis benzoas
USP: Benzyl benzoate

2 Synonyms

Benzoic acid benzyl ester; benzylbenzenecarboxylate; benzyl phenylformate.

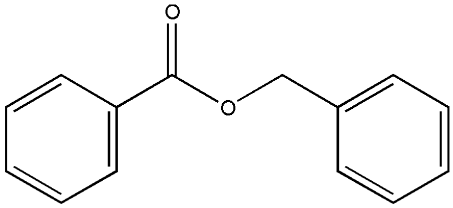
3 Chemical Name and CAS Registry Number

Benzoic acid phenylmethyl ester [120-51-4]

4 Empirical Formula and Molecular Weight

$C_{14}H_{12}O_2$ 212.24

5 Structural Formula



6 Functional Category

Plasticizer; solubilizing agent; solvent; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Benzyl benzoate is used as a solubilizing agent and nonaqueous solvent in intramuscular injections at concentrations of 0.01–46.0% v/v,(1) and as a solvent and plasticizer for cellulose and nitrocellulose. It is also used in the preparation of spray-dried powders using nanocapsules.(2)

However, the most widespread pharmaceutical use of benzyl benzoate is as a topical therapeutic agent in the treatment of scabies.(3) Benzyl benzoate is also used therapeutically as a parasiticide in veterinary medicine.(4)

Other applications of benzyl benzoate include its use as a pediculicide and as a solvent and fixative for flavors and perfumes in cosmetics and food products.

8 Description

Benzyl benzoate is a clear, colorless, oily liquid with a slightly aromatic odor. It produces a sharp, burning sensation on the tongue. At temperatures below 17°C it exists as clear, colorless crystals.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for benzyl benzoate.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	+	+	—
Specific gravity	≈1.123	1.118–1.122	1.116–1.120
Congealing temperature	≈17°C	⩾17.0°C	⩾18.0°C
Boiling point	≈323°C	≈320°C	—
Refractive index	1.568–1.570	1.568–1.570	1.568–1.570
Aldehyde	—	—	⩽0.05%
Acidity	+	+	+
Sulfated ash	⩽0.05%	⩽0.1%	—
Organic volatile impurities	—	—	+
Assay	⩾99.0%	99.0–100.5%	99.0–100.5%

10 Typical Properties

Autoignition temperature: 481°C
Boiling point: 323°C
Flash point: 148°C
Freezing point: 17°C
Refractive index: $n_D^{21} = 1.5681$
Solubility: practically insoluble in glycerin and water; miscible with chloroform, ethanol (95%), ether, and with fatty acids and essential oils.
Specific gravity: 1.12
Vapor density (relative): 7.3 (air = 1)

11 Stability and Storage Conditions

Benzyl benzoate is stable when stored in tight, well-filled, light-resistant containers. Exposure to excessive heat (above 40°C) should be avoided.

12 Incompatibilities

Benzyl benzoate is incompatible with alkalis and oxidizing agents.

13 Method of Manufacture

Benzyl benzoate is a constituent of Peru balsam and occurs naturally in certain plant species. Commercially, benzyl benzoate is produced synthetically by the dry esterification of sodium benzoate and benzoyl chloride in the presence of triethylamine or by the reaction of sodium benzylate with benzaldehyde.

14 Safety

Benzyl benzoate is metabolized by rapid hydrolysis to benzoic acid and benzyl alcohol. Benzyl alcohol is then further metabolized to hippuric acid, which is excreted in the urine.

Benzyl benzoate is widely used as a 25% v/v topical application in the treatment of scabies and as an excipient in intramuscular injections and oral products. Adverse reactions to benzyl benzoate include skin irritation and hypersensitivity reactions. Oral ingestion may cause harmful stimulation of the CNS and convulsions.

LD_{50} (cat, oral): 2.24 g/kg(5–7)
LD_{50} (guinea pig, oral): 1.0 g/kg
LD_{50} (mouse, oral): 1.4 g/kg
LD_{50} (rabbit, oral): 1.68 g/kg
LD_{50} (rabbit, skin): 4.0 g/kg
LD_{50} (rat, oral): 0.5 g/kg
LD_{50} (rat, skin): 4.0 g/kg

15 Handling Precautions

Benzyl benzoate may be harmful if ingested and is irritating to the skin, eyes, and mucous membranes. Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a respirator are recommended. It is recommended that benzyl benzoate is handled in a fume cupboard. Benzyl benzoate is flammable.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IM injections and oral capsules). Included, as an active ingredient, in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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18 Comments

The EINECS number for benzyl benzoate is 204-402-9.

19 Specific References

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21 Authors

E Cahill.

22 Date of Revision

15 August 2005.

Boric Acid

1 Nonproprietary Names

BP: Boric acid
JP: Boric acid
PhEur: Acidum boricum
USPNF: Boric acid

2 Synonyms

Boracic acid; boraic acid; *Borofax*; boron trihydroxide; E284; orthoboric acid; trihydroxyborene.

3 Chemical Name and CAS Registry Number

Orthoboric acid [10043-35-3]
Metaboric acid [13460-50-9]

4 Empirical Formula and Molecular Weight

H_3BO_3	61.83 (for trihydrate)
HBO_2	43.82 (for monohydrate)

5 Structural Formula

H_3BO_3

6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

Boric acid is used as an antimicrobial preservative in eye drops,(1,2) cosmetic products,(3) ointments,(4,5) and topical creams.(6) It is also used as an antimicrobial preservative in foods.

Boric acid has also been used therapeutically in the form of suppositories to treat yeast infections,(7–9) and in dilute concentrations as a mild antiseptic, although it has been superseded by more effective and less toxic disinfectants.(10) *See* Section 14.

Boric acid and borate have good buffering capacity and are used to control pH; they have been used for this purpose in external preparations such as eye drops.(11)

8 Description

Boric acid occurs as a hygroscopic, white crystalline powder, colorless shiny plates, or white crystals.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for boric acid.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Appearance of solution	+	+	—
Loss on drying	≤0.50%	—	≤0.50%
Sulfate	—	≤450 ppm	—
Heavy metals	≤10 ppm	≤15 ppm	≤0.002%
Organic matter	—	+	—
Arsenic	≤5 ppm	—	—
pH	—	3.8–4.8	—
Solubility in alcohol	—	+	+
Assay	≤99.5%	99.5–100.5%	99.5–100.5%

10 Typical Properties

Acidity/alkalinity: pH = 3.5–4.1 (5% w/v aqueous solution)
Density: 1.435
Melting point: 170.9°C. When heated slowly to 181.0°C, boric acid loses water to form metaboric acid (HBO_2); at 140°C, tetraboric acid ($H_2B_4O_7$) is formed; and at higher temperatures, boron trioxide (B_2O_3) is formed.(12)
Solubility: miscible with ethanol, ether, glycerin, water, and other fixed and volatile oils. Solubility in water is increased by addition of hydrochloric, citric, or tartaric acids.
Specific gravity: 1.517

11 Stability and Storage Conditions

Boric acid is hygroscopic and should therefore be stored in an air-tight, sealed container. The container must be labeled ‘Not for Internal Use’.

12 Incompatibilities

Boric acid is incompatible with water, strong bases and alkali metals. It reacts violently with potassium and acid anhydrides. It also forms a complex with glycerin, which is a stronger acid than boric acid.

13 Method of Manufacture

Boric acid occurs naturally as the mineral sassolite. However, the majority of boric acid is produced by reacting inorganic borates with sulfuric acid in an aqueous medium. Sodium borate and partially refined calcium borate (colemanite) are the principal raw materials. When boric acid is made from colemanite, the fine-ground ore is vigorously stirred with mother liquor and sulfuric acid at about 90°C. The by-product calcium sulfate is removed by filtration, and the boric acid is crystallized by cooling the filtrate.

14 Safety

Boric acid is a weak bacteriostatic and antimicrobial agent, and has been used in topical preparations such as eye lotions, mouthwashes and gargles. It has also been used in US- and Japanese-approved intravenous products. Solutions of boric acid were formerly used to wash out body cavities, and as applications to wounds and ulcers, although the use of boric acid for these purposes is now regarded as inadvisable owing to the possibility of absorption.(13) Boric acid is not used internally owing to its toxicity. It is poisonous by ingestion and moderately toxic by skin contact. Experimentally it has proved to be toxic by inhalation and subcutaneous routes, and moderately toxic by intraperitoneal and intravenous routes.

Boric acid is absorbed from the gastrointestinal tract and from damaged skin, wounds, and mucous membranes, although it does not readily permeate intact skin. The main symptoms of boric acid poisoning are abdominal pain, diarrhea, erythematous rash involving both skin and mucous membrane, and vomiting. These symptoms may be followed by desquamation, and stimulation or depression of the central nervous system. Convulsions, hyperpyrexia, and renal tubular damage have been known to occur.

Death has occurred from ingestion of less than 5 g in young children, and of 5–20 g in adults. Fatalities have occurred most frequently in young children after the accidental ingestion of solutions of boric acid, or after the application of boric acid powder to abraded skin.

The permissible exposure limit (PEL) of boric acid is 15 mg/m^3 total dust, and 5 mg/m^3 respirable fraction for nuisance dusts.(14)

LD_{50} (mouse, oral): 3.45 g/kg(15)
LD_{50} (mouse, IV): 1.24 g/kg
LD_{50} (mouse, SC): 1.74 g/kg
LD_{50} (rat, oral): 2.660 g/kg
LD_{50} (rat, IV): 1.33 g/kg
LD_{50} (rat, SC): 1.4 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Boric acid is irritating to the skin and is potentially toxic by inhalation. Gloves, eye protection, protective clothing, and a respirator are recommended.

16 Regulatory Status

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IV injections; ophthalmic preparations; otic solutions; topical preparations). Reported in the EPA TSCA Inventory. In the UK, the use of boric acid in cosmetics and toiletries is restricted. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Sodium borate.

18 Comments

Boric acid has been used experimentally as a model oxo-acid to retard mannitol crystallization in the solid state.(16)

The EINECS number for boric acid is 233-139-2.

19 Specific References

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20 General References

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21 Authors

M Yelvigi.

22 Date of Revision

15 August 2005.

Bronopol

1 Nonproprietary Names

BP: Bronopol

2 Synonyms

2-Bromo-2-nitro-1,3-propanediol; β-bromo-β-nitrotrimethyleneglycol; *Myacide*.

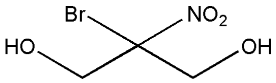
3 Chemical Name and CAS Registry Number

2-Bromo-2-nitropropane-1,3-diol [52-51-7]

4 Empirical Formula and Molecular Weight

$C_3H_6BrNO_4$ 200.00

5 Structural Formula



6 Functional Category

Antimicrobial preservative; antiseptic.

7 Applications in Pharmaceutical Formulation or Technology

Bronopol 0.01–0.1% w/v is used as an antimicrobial preservative either alone or in combination with other preservatives in topical pharmaceutical formulations, cosmetics, and toiletries; the usual concentration is 0.02% w/v.

8 Description

Bronopol is a white or almost white crystalline powder; odorless or with a faint characteristic odor.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for bronopol.

Test	BP 2004
Identification	+
Characters	+
Acidity or alkalinity (1% w/v solution)	5.0–7.0
Related substances	+
Sulfated ash	⩽0.1%
Water	⩽0.5%
Assay (anhydrous basis)	99.0–101.0%

10 Typical Properties

Antimicrobial activity: bronopol is active against both Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*, with typical minimum inhibitory concentrations (MICs) between 10–50 μg/mL;(1–8) *see also* Table II. At room temperature, a 0.08% w/v aqueous solution may reduce the viability of culture collection strains of *Escherichia coli* and *Pseudomonas aeruginosa* by 100-fold or more in 15 minutes. Antimicrobial activity is not markedly influenced by pH in the range 5.0–8.0, nor by common anionic and nonionic surfactants, lecithin, or proteins.(2,5,6) Bronopol is less active against yeasts and molds, with typical MICs of 50–400 μg/mL or more, and has little or no useful activity against bacterial spores. *See also* Section 12.

Table II: Minimum inhibitory concentrations (MICs) of bronopol.(2,9)

Microorganism	MIC (μg/mL)
Aspergillus niger	3200
Bacillus subtilis	12.5
Burkholderia (Pseudomonas) cepacia	25
Candida albicans	1600
Escherichia coli	12.5–50
Klebsiella aerogenes	25
Legionella pneumophilia	50
Penicillium roqueforti	400
Penicillium funiculosum	1600
Pityrosporum ovale	125
Proteus mirabilis	25–50
Proteus vulgaris	12.5–50
Pseudomonas aeruginosa	12.5–50
Saccharomyces cerevisiae	3200
Salmonella gallinarum	25
Staphylococcus aureus	12.5–50
Staphylococcus epidermidis	50
Streptococcus faecalis	50
Trichophyton mentagrophytes	200
Trichoderma viride	6400

Melting point: 128–132°C
Partition coefficients:
Mineral oil : water = 0.043 at 22–24°C;
Peanut oil : water = 0.11 at 22–24°C.
Solubility: *see* Table III.

Table III: Solubility of bronopol.

Solvent	Solubility at 20°C
Cottonseed oil	Slightly soluble
Ethanol (95%)	1 in 2
Glycerol	1 in 100
Isopropyl myristate	1 in 200
Mineral oil	Slightly soluble
Propan-2-ol	1 in 4
Propylene glycol	1 in 2
Water	1 in 4

11 Stability and Storage Conditions

Bronopol is stable and its antimicrobial activity is practically unaffected when stored as a solid at room temperature and ambient relative humidity for up to 2 years.(3)

The pH of a 1.0% w/v aqueous solution is 5.0–6.0 and falls slowly during storage; solutions are more stable in acid conditions. Half-lives of bronopol in buffered aqueous solutions at 0.03% w/v are shown in Table IV.(9)

Microbiological assay results indicate longer half-lives than those obtained by HPLC and thus suggest that degradation products may contribute to antimicrobial activity. Formaldehyde and nitrites are among the decomposition products, but formaldehyde arises in such low concentrations that its antimicrobial effect is not likely to be significant. On exposure to light, especially under alkaline conditions, solutions become yellow or brown-colored but the degree of discoloration does not directly correlate with loss of antimicrobial activity.

The bulk material should be stored in a well-closed, nonaluminum container protected from light, in a cool, dry place.

Table IV: Half-lives of bronopol under different storage conditions.

Temperature (°C)	pH 4	pH 6	pH 8
5	>5 years	>5 years	6 months
25	>5 years	>5 years	4 months
40	2 years	4 months	8 days
60	2 weeks	<2 days	<1 day

12 Incompatibilities

Sulfhydryl compounds cause significant reductions in the activity of bronopol, and cysteine hydrochloride may be used as the deactivating agent in preservative efficacy tests; lecithin/polysorbate combinations are unsuitable for this purpose.(5) Bronopol is incompatible with sodium thiosulfate, with sodium metabisulfite, and with amine oxide or protein hydrolysate surfactants. Owing to an incompatibility with aluminum, the use of aluminum in the packaging of products that contain bronopol should be avoided.

13 Method of Manufacture

Bronopol is synthesized by the reaction of nitromethane with paraformaldehyde in an alkaline environment, followed by bromination. After crystallization, bronopol powder may be milled to produce a powder of the required fineness.

14 Safety

Bronopol is used widely in topical pharmaceutical formulations and cosmetics as an antimicrobial preservative.

Although bronopol has been reported to cause both irritant and hypersensitivity adverse reactions following topical use,(10–13) it is generally regarded as a nonirritant and nonsensitizing material at concentrations up to 0.1% w/v. At a concentration of 0.02% w/v, bronopol is frequently used as a preservative in ‘hypoallergenic’ formulations.

Animal toxicity studies have shown no evidence of phototoxicity or tumor occurrence when bronopol is applied to rodents topically or administered orally; and there is no *in vitro* or *in vivo* evidence of mutagenicity;(1) this is despite the demonstrated potential of bronopol to liberate nitrite on decomposition, which in the presence of certain amines may generate nitrosamines. Formation of nitrosamines in formulations containing amines may be reduced by limiting the concentration of bronopol to 0.01% w/v and including an antioxidant such as 0.2% w/v alpha tocopherol or 0.05% w/v butylated hydroxytoluene;(14) other inhibitor systems may also be appropriate.(15)

LD_{50} (dog, oral): 250 mg/kg (16)
LD_{50} (mouse, IP): 15.5 mg/kg
LD_{50} (mouse, IV): 48 mg/kg
LD_{50} (mouse, oral): 270 mg/kg
LD_{50} (mouse, SC): 116 mg/kg
LD_{50} (mouse, skin): 4.75 g/kg
LD_{50} (rat, IP): 26 mg/kg
LD_{50} (rat, IV): 37.4 mg/kg
LD_{50} (rat, oral): 180 mg/kg
LD_{50} (rat, SC): 170 mg/kg
LD_{50} (rat, skin): 1.6 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Bronopol may be harmful upon inhalation and the solid or concentrated solutions can be irritant to the skin and eyes. Eye protection, gloves, and dust respirator are recommended. Bronopol burns to produce toxic fumes.

16 Regulatory Status

Included in topical pharmaceutical formulations licensed in Europe. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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18 Comments

Bronopol owes its usefulness as a preservative largely to its activity against *Pseudomonas aeruginosa*, and its affinity for polar solvents, which prevents the loss of preservative into the oil phase of emulsions that is seen with some other preservatives. Other advantages include a low incidence of microbial resistance; low concentration exponent;(17) and good compatibility with most surfactants, other excipients, and preservatives, with which it can therefore be used in combination.

The major disadvantages of bronopol are relatively poor activity against yeasts and molds, instability at alkaline pH, and the production of formaldehyde and nitrite on decomposition, although there is no evidence of serious toxicity problems associated with bronopol that are attributable to these compounds.

The EINECS number for bronopol is 200-143-0.

19 Specific References

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Toler JC. Preservative stability and preservative systems. *Int J Cosmet Sci* 1985; **7**: 157–164.

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21 Authors

SP Denyer, NA Hodges.

22 Date of Revision

15 August 2005.

Butylated Hydroxyanisole

1 Nonproprietary Names

BP: Butylated hydroxyanisole
PhEur: Butylhydroxyanisolum
USPNF: Butylated hydroxyanisole

2 Synonyms

BHA; *tert*-butyl-4-methoxyphenol; 1,1-dimethylethyl-4-methoxyphenol; E320; *Nipanox BHA*; *Nipantiox 1-F*; *Tenox BHA*.

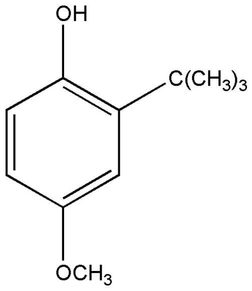
3 Chemical Name and CAS Registry Number

2-*tert*-Butyl-4-methoxyphenol [25013-16-5]

4 Empirical Formula and Molecular Weight

$C_{11}H_{16}O_2$ 180.25
The PhEur 2005 describes butylated hydroxyanisole as 2-(1,1-dimethylethyl)-4-methoxyphenol containing not more than 10% of 3-(1,1-dimethylethyl)-4-methoxyphenol.

5 Structural Formula



6 Functional Category

Antioxidant.

7 Applications in Pharmaceutical Formulation or Technology

Butylated hydroxyanisole is an antioxidant (*see* Table I) with some antimicrobial properties.(1) It is used in a wide range of cosmetics, foods, and pharmaceuticals. When used in foods, it is used to delay or prevent oxidative rancidity of fats and oils and to prevent loss of activity of oil-soluble vitamins.

Butylated hydroxyanisole is frequently used in combination with other antioxidants, particularly butylated hydroxytoluene and alkyl gallates, and with sequestrants or synergists such as citric acid.

FDA regulations direct that the total content of antioxidant in vegetable oils and direct food additives shall not exceed 0.02% w/w (200 ppm) of fat or oil content or essential (volatile) oil content of food.

USDA regulations require that the total content of antioxidant shall not exceed 0.01% w/w (100 ppm) of any one antioxidant or 0.02% w/w combined total of any antioxidant combination in animal fats.

Japanese regulations allow up to 1 g/kg in animal fats.

Table I: Antioxidant uses of butylated hydroxyanisole.

Antioxidant use	Concentration (%)
β-Carotene	0.01
Essential oils and flavoring agents	0.02–0.5
IM injections	0.03
IV injections	0.0002–0.0005
Oils and fats	0.02
Topical formulations	0.005–0.02
Vitamin A	10 mg per million units

8 Description

Butylated hydroxyanisole occurs as a white or almost white crystalline powder or a yellowish-white waxy solid with a faint, characteristic aromatic odor.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for butylated hydroxyanisole.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Residue on ignition	—	⩽0.01%
Sulfated ash	⩽0.1%	—
Related substances	+	—
Heavy metals	⩽10 ppm	⩽0.001%
Organic volatile impurities	—	+
Assay	—	⩾98.5%

10 Typical Properties

Antimicrobial activity: activity is similar to that of the *p*-hydroxybenzoate esters (parabens). The greatest activity is against molds and Gram-positive bacteria, with less activity against Gram-negative bacteria.
Boiling point: 264°C at 745 mmHg
Density (true): 1.117 g/cm^3
Flash point: 130°C
Melting point: 47°C (for pure 2-*tert*-butyl-4-methoxyphenol); *see also* Section 18.
Solubility: practically insoluble in water; soluble in methanol; freely soluble in ⩾50% aqueous ethanol, propylene glycol, chloroform, ether, hexane, cottonseed oil, peanut oil, soybean oil, glyceryl monooleate, and lard, and in solutions of alkali hydroxides.
Viscosity (kinematic): 3.3 mm^2/s (3.3 cSt) at 99°C.

11 Stability and Storage Conditions

Exposure to light causes discoloration and loss of activity. Butylated hydroxyanisole should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

Butylated hydroxyanisole is phenolic and undergoes reactions characteristic of phenols. It is incompatible with oxidizing agents and ferric salts. Trace quantities of metals and exposure to light cause discoloration and loss of activity.

13 Method of Manufacture

Prepared by the reaction of *p*-methoxyphenol with isobutene.

14 Safety

Butylated hydroxyanisole is absorbed from the gastrointestinal tract and is metabolized and excreted in the urine with less than 1% unchanged within 24 hours of ingestion.(2) Although there have been some isolated reports of adverse skin reactions to butylated hydroxyanisole,(3,4) it is generally regarded as nonirritant and nonsensitizing at the levels employed as an antioxidant.

Concern over the use of butylated hydroxyanisole has occurred following long-term animal feeding studies. Although previous studies in rats and mice fed butylated hydroxyanisole at several hundred times the US-permitted level in the human diet showed no adverse effects, a study in which rats, hamsters, and mice were fed butylated hydroxyanisole at 1–2% of the diet produced benign and malignant tumors of the forestomach, but in no other sites. However, humans do not have any region of the stomach comparable to the rodent forestomach and studies in animals that also do not have a comparable organ (dogs, monkeys, and guinea pigs) showed no adverse effects. Thus, the weight of evidence does not support any relevance to the human diet where butylated hydroxyanisole is ingested at much lower levels.(5) The WHO acceptable daily intake of butylated hydroxyanisole has been set at 500 μg/kg body-weight.(5)

LD_{50} (mouse, oral): 1.1–2.0 g/kg(6)
LD_{50} (rabbit, oral): 2.1 g/kg
LD_{50} (rat, IP): 0.88 g/kg
LD_{50} (rat, oral): 2.0 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Butylated hydroxyanisole may be irritant to the eyes and skin and on inhalation. It should be handled in a well-ventilated environment; gloves and eye protection are recommended. On combustion, toxic fumes may be given off.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IM and IV injections, nasal sprays, oral capsules and tablets, and sublingual, rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Butylated hydroxytoluene.

18 Comments

The commercially available material can have a wide melting point range (47–57°C) owing to the presence of varying amounts of 3-*tert*-butyl-4-methoxyphenol.

Tenox brands contain 0.1% w/w citric acid as a stabilizer.

A specification for butylated hydroxyanisole is contained in the Food Chemicals Codex (FCC).

The EINECS number for butylated hydroxyanisole is 246-563-8.

19 Specific References

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2 El-Rashidy R, Niazi S. A new metabolite of butylated hydroxyanisole in man. *Biopharm Drug Dispos* 1983; **4**: 389–396.
3 Roed-Peterson J, Hjorth N. Contact dermatitis from antioxidants: hidden sensitizers in topical medications and foods. *Br J Dermatol* 1976; **94**: 233–241.
4 Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. *Br J Dermatol* 1981; **104**: 369–381.
5 FAO/WHO. Evaluation of certain food additives and contaminants. Thirty-third report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1989; No. 776.
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20 General References

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Verhagen H. Toxicology of the food additives BHA and BHT. *Pharm Weekbl Sci* 1990; **12**: 164–166.

21 Authors

RT Guest.

22 Date of Revision

23 August 2005.

Butylated Hydroxytoluene

1 Nonproprietary Names

BP: Butylated hydroxytoluene
PhEur: Butylhydroxytoluenum
USPNF: Butylated hydroxytoluene

2 Synonyms

Agidol; BHT; 2,6-bis(1,1-dimethylethyl)-4-methylphenol; butylhydroxytoluene; *Dalpac*; dibutylated hydroxytoluene; 2,6-di-*tert*-butyl-*p*-cresol; 3,5-di-*tert*-butyl-4-hydroxytoluene; E321; *Embanox BHT*; *Impruvol*; *Ionol CP*; *Nipanox BHT*; *OHS28890*; *Sustane*; *Tenox BHT*; *Topanol*; *Vianol*.

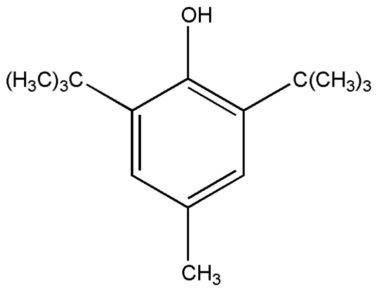
3 Chemical Name and CAS Registry Number

2,6-Di-*tert*-butyl-4-methylphenol [128-37-0]

4 Empirical Formula and Molecular Weight

$C_{15}H_{24}O$ 220.35

5 Structural Formula



6 Functional Category

Antioxidant.

7 Applications in Pharmaceutical Formulation or Technology

Butylated hydroxytoluene is used as an antioxidant (*see* Table I) in cosmetics, foods, and pharmaceuticals. It is mainly used to delay or prevent the oxidative rancidity of fats and oils and to prevent loss of activity of oil-soluble vitamins.

Butylated hydroxytoluene is also used at 0.5–1.0% w/w concentration in natural or synthetic rubber to provide enhanced color stability.

Butylated hydroxytoluene has some antiviral activity$^{(1)}$ and has been used therapeutically to treat herpes simplex labialis.$^{(2)}$

8 Description

Butylated hydroxytoluene occurs as a white or pale yellow crystalline solid or powder with a faint characteristic odor.

Table I: Antioxidant uses of butylated hydroxytoluene.

Antioxidant use	Concentration (%)
β-Carotene	0.01
Edible vegetable oils	0.01
Essential oils and flavoring agents	0.02–0.5
Fats and oils	0.02
Fish oils	0.01–0.1
Inhalations	0.01
IM injections	0.03
IV injections	0.0009–0.002
Topical formulations	0.0075–0.1
Vitamin A	10 mg per million units

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for butylated hydroxytoluene.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Congealing temperature	—	⩾69.2°C
Freezing point	69–70°C	—
Residue on ignition	—	⩽0.002%
Sulfated ash	⩽0.1%	—
Heavy metals	—	⩽0.001%
Organic volatile impurities	—	+
Related substances	+	—
Assay	—	⩾99.0%

10 Typical Properties

Boiling point: 265°C
Density (bulk): 0.48–0.60 g/cm^3
Density (true): 1.031 g/cm^3
Flash point: 127°C (open cup)
Melting point: 70°C
Moisture content: ⩽0.05%
Partition coefficient: Octanol : water = 4.17–5.80
Refractive index: n_D^{75} = 1.4859
Solubility: practically insoluble in water, glycerin, propylene glycol, solutions of alkali hydroxides, and dilute aqueous mineral acids. Freely soluble in acetone, benzene, ethanol (95%), ether, methanol, toluene, fixed oils, and mineral oil. More soluble than butylated hydroxyanisole in food oils and fats.
Specific gravity:
1.006 at 20°C;
0.890 at 80°C;
0.883 at 90°C;
0.800 at 100°C.
Specific heat:
1.63 J/g/°C (0.39 cal/g/°C) for solid;

2.05 J/g/°C (0.49 cal/g/°C) for liquid.

Vapor density (relative): 7.6 (air = 1)

Vapor pressure:

1.33 Pa (0.01 mmHg) at 20°C;
266.6 Pa (2 mmHg) at 100°C.

Viscosity (kinematic): 3.47 mm^2/s (3.47 cSt) at 80°C.

11 Stability and Storage Conditions

Exposure to light, moisture, and heat causes discoloration and a loss of activity. Butylated hydroxytoluene should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

Butylated hydroxytoluene is phenolic and undergoes reactions characteristic of phenols. It is incompatible with strong oxidizing agents such as peroxides and permanganates. Contact with oxidizing agents may cause spontaneous combustion. Iron salts cause discoloration with loss of activity. Heating with catalytic amounts of acids causes rapid decomposition with the release of the flammable gas isobutene.

13 Method of Manufacture

Prepared by the reaction of *p*-cresol with isobutene.

14 Safety

Butylated hydroxytoluene is readily absorbed from the gastrointestinal tract and is metabolized and excreted in the urine mainly as glucuronide conjugates of oxidation products. Although there have been some isolated reports of adverse skin reactions, butylated hydroxytoluene is generally regarded as nonirritant and nonsensitizing at the levels employed as an antioxidant.(3,4)

The WHO has set a temporary estimated acceptable daily intake for butylated hydroxytoluene at up to 125 μg/kg body-weight.(5)

Ingestion of 4 g of butylated hydroxytoluene, although causing severe nausea and vomiting, has been reported to be nonfatal.(6)

LD_{50} (guinea pig, oral): 10.7 g/kg(7)
LD_{50} (mouse, IP): 0.14 g/kg
LD_{50} (mouse, IV): 0.18 g/kg
LD_{50} (mouse, oral): 0.65 g/kg
LD_{50} (rat, oral): 0.89 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Butylated hydroxytoluene may be irritant to the eyes and skin and on inhalation. It should be handled in a well-ventilated environment; gloves and eye protection are recommended. Closed containers may explode owing to pressure build-up when exposed to extreme heat.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IM and IV injections, nasal sprays, oral capsules and tablets, rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Butylated hydroxyanisole.

18 Comments

A specification for butylated hydroxytoluene is contained in the Food Chemicals Codex (FCC).

The EINECS number for butylated hydroxytoluene is 204-881-4.

19 Specific References

1 Snipes W, Person S, Keith A, Cupp J. Butylated hydroxytoluene inactivates lipid-containing viruses. *Science* 1975; **188**: 64–66.
2 Freeman DJ, Wenerstrom G, Spruance SL. Treatment of recurrent herpes simplex labialis with topical butylated hydroxytoluene. *Clin Pharmacol Ther* 1985; **38**: 56–59.
3 Roed-Peterson J, Hjorth N. Contact dermatitis from antioxidants: hidden sensitizers in topical medications and foods. *Br J Dermatol* 1976; **94**: 233–241.
4 Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. *Br J Dermatol* 1981; **104**: 369–381.
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6 Shlian DM, Goldstone J. Toxicity of butylated hydroxytoluene. *N Engl J Med* 1986; **314**: 648–649.
7 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 430.

20 General References

Verhagen H. Toxicology of the food additives BHA and BHT. *Pharm Weekbl (Sci)* 1990; **12**: 164–166.

21 Authors

RT Guest.

22 Date of Revision

23 August 2005.

Butylparaben

1 Nonproprietary Names

BP: Butyl hydroxybenzoate
JP: Butyl parahydroxybenzoate
PhEur: Butylis parahydroxybenzoas
USPNF: Butylparaben

2 Synonyms

4-Hydroxybenzoic acid butyl ester; *Lexgard B*; *Nipabutyl*; *Tegosept B*; *Trisept B*; *Uniphen P-23*; *Unisept B*.

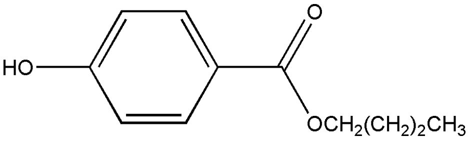
3 Chemical Name and CAS Registry Number

Butyl-4-hydroxybenzoate [94-26-8]

4 Empirical Formula and Molecular Weight

$C_{11}H_{14}O_3$ 194.23

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

Butylparaben is widely used as an antimicrobial preservative in cosmetics and pharmaceutical formulations; *see* Table I.

It may be used either alone or in combination with other paraben esters or with other antimicrobial agents. In cosmetics, it is the fourth most frequently used preservative.(1)

As a group, the parabens are effective over a wide pH range and have a broad spectrum of antimicrobial activity, although they are most effective against yeasts and molds; *see* Section 10.

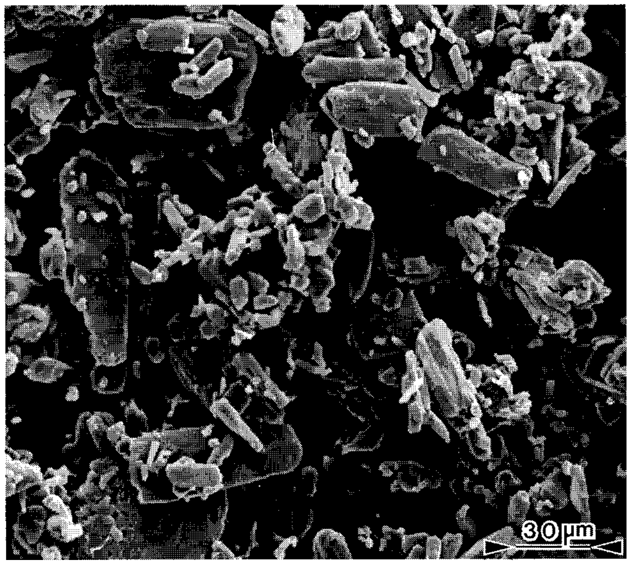
Owing to the poor solubility of the parabens, paraben salts, particularly the sodium salt, are frequently used in formulations. However, this may raise the pH of poorly buffered formulations.

See Methylparaben for further information.

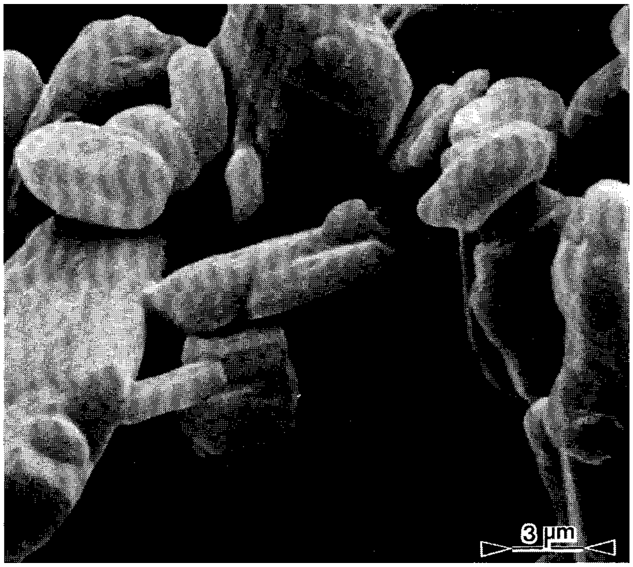
Table I: Uses of butylparaben.

Use	Concentration (%)
Oral suspensions	0.006–0.05
Topical preparations	0.02–0.4

SEM: 1
Excipient: Butylparaben
Magnification: 240×



SEM: 2
Excipient: Butylparaben
Magnification: 2400×



8 Description

Butylparaben occurs as colorless crystals or a white, crystalline, odorless or almost odorless, tasteless powder.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for butylparaben.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	+	+	—
Appearance of solution	—	+	—
Melting range	69–72°C	68–71°C	68–72°C
Acidity	—	+	+
Loss on drying	⩽0.5%	—	⩽0.5%
Residue on ignition	⩽0.1%	—	⩽0.05%
Sulfated ash	—	⩽0.1%	—
Related substances	—	+	—
Chloride	⩽0.035%	—	—
Sulfate	⩽0.024%	—	—
Heavy metals	⩽20 ppm	—	—
Readily carbonizable substances	+	—	—
Parahydroxybenzoic acid and salicylic acid	+	—	—
Organic volatile impurities	—	—	+
Assay (dried basis)	⩾99.0%	98.0–102.0%	99.0–100.5%

10 Typical Properties

Antimicrobial activity: butylparaben exhibits antimicrobial activity between pH 4–8. Preservative efficacy decreases with increasing pH owing to the formation of the phenolate anion. Parabens are more active against yeasts and molds than against bacteria. They are also more active against Gram-positive than against Gram-negative bacteria; *see* Table III.(2)

The activity of the parabens increases with increasing chain length of the alkyl moiety, but solubility decreases. Butylparaben is thus more active than methylparaben. Activity may be improved by using combinations of parabens since synergistic effects occur. Activity has also been reported to be improved by the addition of other excipients; *see* Methylparaben for further information.

Table III: Minimum inhibitory concentrations (MICs) for butylparaben in aqueous solution.(2)

Microorganism	MIC (μg/mL)
Aerobacter aerogenes ATCC 8308	400
Aspergillus niger ATCC 9642	125
Aspergillus niger ATCC 10254	200
Bacillus cereus var. *mycoides* ATCC 6462	63
Bacillus subtilis ATCC 6633	250
Candida albicans ATCC 10231	125
Enterobacter cloacae ATCC 23355	250
Escherichia coli ATCC 8739	5000
Escherichia coli ATCC 9637	5000
Klebsiella pneumoniae ATCC 8308	250
Penicillium chrysogenum ATCC 9480	70
Penicillium digitatum ATCC 10030	32
Proteus vulgaris ATCC 13315	125
Pseudomonas aeruginosa ATCC 9027	>1000
Pseudomonas aeruginosa ATCC 15442	>1000
Pseudomonas stutzeri	500
Rhizopus nigricans ATCC 6227A	63
Saccharomyces cerevisiae ATCC 9763	35
Salmonella typhosa ATCC 6539	500
Serratia marcescens ATCC 8100	500
Staphylococcus aureus ATCC 6538P	125
Staphylococcus epidermidis ATCC 12228	250
Trichophyton mentagrophytes	35

Density (bulk): $0.731\ g/cm^3$

Density (tapped): $0.819\ g/cm^3$

Melting point: 68–72°C

Partition coefficients: values for different vegetable oils vary considerably and are affected by the purity of the oil; *see* Table IV.(3)

Solubility: see Table V.

Table IV: Partition coefficients for butylparaben between oils and water.(3)

Solvent	Partition coefficient oil : water
Mineral oil	3.0
Peanut oil	280
Soybean oil	280

Table V: Solubility of butylparaben.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	Freely soluble
Ethanol	1 in 0.5
Ethanol (95%)	1 in 1
Ether	Freely soluble
Glycerin	1 in 330
Methanol	1 in 0.5
Mineral oil	1 in 1000
Peanut oil	1 in 20
Propylene glycol	1 in 1
Water	1 in >5000 1 in 670 at 80°C

11 Stability and Storage Conditions

Aqueous butylparaben solutions at pH 3–6 can be sterilized by autoclaving, without decomposition.(4) At pH 3–6, aqueous solutions are stable (less than 10% decomposition) for up to about 4 years at room temperature, while solutions at pH 8 or above are subject to rapid hydrolysis (10% or more after about 60 days at room temperature).(5)

Butylparaben should be stored in a well-closed container, in a cool, dry place.

12 Incompatibilities

The antimicrobial activity of butylparaben is considerably reduced in the presence of nonionic surfactants as a result of micellization.(6) Absorption of butylparaben by plastics has not been reported but appears probable given the behavior of other parabens. Some pigments, e.g., ultramarine blue and yellow iron oxide, absorb butylparaben and thus reduce its preservative properties.(7)

Butylparaben is discolored in the presence of iron and is subject to hydrolysis by weak alkalis and strong acids.

See also Methylparaben.

13 Method of Manufacture

Butylparaben is prepared by esterification of *p*-hydroxybenzoic acid with *n*-butanol.

14 Safety

Butylparaben and other parabens are widely used as antimicrobial preservatives in cosmetics and oral and topical pharmaceutical formulations.

Systemically, no adverse reactions to parabens have been reported, although they have been associated with hypersensitivity reactions. *See* Methylparaben for further information.

LD_{50} (mouse, IP): 0.23 g/kg(8)
LD_{50} (mouse, oral): 13.2 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Butylparaben may be irritant to the skin, eyes, and mucous membranes and should be handled in a well-ventilated environment. Eye protection, gloves, and a dust mask or respirator are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (injections, oral capsules, solutions, suspensions, syrups and tablets, rectal, and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Butylparaben sodium; ethylparaben; methylparaben; propylparaben.

Butylparaben sodium

Empirical formula: $C_{11}H_{13}NaO_3$
Molecular weight: 216.23
CAS number: [36457-20-2]
Synonyms: butyl-4-hydroxybenzoate sodium salt; sodium butyl hydroxybenzoate.
Appearance: white, odorless or almost odorless, hygroscopic powder.
Acidity/alkalinity: pH = 9.5–10.5 (0.1% w/v aqueous solution)
Solubility: 1 in 10 of ethanol (95%); 1 in 1 of water.
Comments: butylparaben sodium may be used instead of butylparaben because of its greater aqueous solubility. In unbuffered formulations, pH adjustment may be required.

18 Comments

See Methylparaben for further information and references.

The EINECS number for butylparaben is 202-318-7.

19 Specific References

1 Decker RL, Wenninger JA. Frequency of preservative use in cosmetic formulas as disclosed to FDA—1987. *Cosmet Toilet* 1987; **102**(12): 21–24.
2 Haag TE, Loncrini DF. Esters of para-hydroxybenzoic acid. In: Kabara JJ, ed. *Cosmetic and Drug Preservation.* New York: Marcel Dekker, 1984: 63–77.
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4 Aalto TR, Firman MC, Rigler NE. *p*-Hydroxybenzoic acid esters as preservatives I: uses, antibacterial and antifungal studies, properties and determination. *J Am Pharm Assoc (Sci)* 1953; **42**: 449–457.
5 Kamada A, Yata N, Kubo K, Arakawa M. Stability of *p*-hydroxybenzoic acid esters in acidic medium. *Chem Pharm Bull* 1973; **21**: 2073–2076.
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8 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 637.

See also Methylparaben.

20 General References

Golightly LK, Smolinske SS, Bennett ML, *et al.* Pharmaceutical excipients associated with inactive ingredients in drug products (part I). *Med Toxicol* 1988; **3**: 128–165.

See also Methylparaben.

21 Authors

R Johnson, R Steer.

22 Date of Revision

23 August 2005.

Calcium Alginate

1 Nonproprietary Names

None adopted.

2 Synonyms

Alginic acid; calcium salt; *Algin*; *CA33*; calc algin; calcium polymannuronate; *Calginate*; E404; *Kaltostat*.

3 Chemical Name and CAS Registry Number

Calcium alginate [9005-35-0]

4 Empirical Formula and Molecular Weight

$[(C_6H_7O_6)_2Ca]_n$ 195.16 (calculated)
219.00 (actual, average)

Each calcium ion binds with two alginate molecules. The molecular weight of 195.16 relates to one alginate molecule, and the equivalent of half a calcium ion, therefore n = ½.

Calcium alginate is a polyuronide made up of a sequence of two hexuronic acid residues, namely D-mannuronic acid and L-guluronic acid. The two sugars form blocks of up to 20 units along the chain, with the proportion of the blocks dependent on the species of seaweed and also the part of the seaweed used. The number and length of the blocks are important in determining the physical properties of the alginate produced; the number and sequence of the mannuronate and guluronate residues varies in the naturally occurring alginate.

It has a typical macromolecular weight between 10 000 and 600 000.

5 Structural Formula

See Section 4.

6 Functional Category

Emulsifiying agent; stabilizing agent; tablet disintegrant; thickener.

7 Applications in Pharmaceutical Formulation or Technology

In pharmaceutical formulations, calcium alginate and calcium-sodium alginate have been used as tablet disintegrants.(1) The use of a high concentration (10%) of calcium-sodium alginate has been reported to cause slight speckling of tablets.(1)

A range of different types of delivery systems intended for oral administration have been investigated. These exploit the gelling properties of calcium alginate.(2) Calcium alginate beads have been used to prepare floating dosage systems(3,4) containing amoxicillin,(5) frusemide,(6) and barium sulfate;(7) and as a means of providing a sustained or controlled-release action for sulindac,(8) diclofenac,(9,10) tiaramide,(11) insulin,(12) and ampicillin.(13) The use of calcium alginate beads, reinforced with chitosan, may be useful for the controlled release of protein drugs to the gastro-intestinal tract.(14) The bioadhesive properties of calcium alginate beads have also been investigated.(15)

A series of studies investigating the production,(16) formulation,(17) and drug release(18) from calcium alginate matrices for oral administration have been published. The release of diltiazem hydrochloride from a polyvinyl alcohol matrix was shown to be controlled by coating with a calcium alginate membrane; the drug release profile could be modified by increasing the coating thickness of the calcium alginate layer.(19) The microencapsulation of live attenuated Bacillus Calmette–Guérin (BCG) cells within a calcium alginate matrix has also been reported.(20)

It has been shown that a modified drug release can be obtained from calcium alginate microcapsules,(21) pellets,(22,23) and microspheres.(24) When biodegradable bone implants composed of calcium alginate spheres and containing gentamicin were introduced into the femur of rats, effective drug levels in bone and soft tissue were obtained for 30 days and 7 days, respectively.(25)

Therapeutically, the gelling properties of calcium alginate are utilized in wound dressings in the treatment of leg ulcers, pressure sores, and other exuding wounds. These dressings are highly absorbent and are suitable for moderately or heavily exuding wounds. Calcium alginate dressings also have hemostatic properties, with calcium ions being exchanged for sodium ions in the blood; this stimulates both platelet activation and whole blood coagulation. A mixed calcium–sodium salt of alginic acid is used as fibers in dressings or wound packing material.

Sterile powder consisting of a mixture of calcium and sodium alginates has been used in place of talc in glove powders.

In foods, calcium alginate is used as an emulsifier, thickener, and stabilizer.

8 Description

Calcium alginate is an odorless or almost odorless, tasteless, white to pale yellowish-brown powder or fibers.

9 Pharmacopeial Specifications

See Section 18.

10 Typical Properties

Moisture content: loses not more than 22% of its weight on drying.

Solubility: practically insoluble in chloroform, ethanol, ether, water, and other organic solvents. Soluble in dilute solutions of sodium citrate and of sodium bicarbonate and in sodium chloride solution. Soluble in alkaline solutions or in solutions of substances that combine with calcium.

11 Stability and Storage Conditions

Calcium alginate can be sterilized by autoclaving at 115°C for 30 minutes or by dry heat at 150°C for 1 hour. Calcium alginate should be stored in airtight containers.

12 Incompatibilities

Calcium alginate is incompatible with alkalis and alkali salts. Propranolol hydrochloride has been shown to bind to alginate molecules, suggesting that propranolol and calcium ions share common binding sites in the alginate chains; the formation of the calcium alginate gel structure was impeded in the presence of propranolol molecules.(26)

13 Method of Manufacture

Calcium alginate can be obtained from seaweed, mainly species of *Laminaria*.

Solutions of sodium alginate interact with an ionized calcium salt, resulting in the instantaneous precipitation of insoluble calcium alginate, which can then be further processed. Introducing varying proportions of sodium ions during manufacture can produce products having different absorption rates.

14 Safety

Calcium alginate is widely used in oral and topical formulations, and in foods.

In 1974, the WHO set an estimated acceptable daily intake of calcium alginate of up to 25 mg, as alginic acid, per kilogram body-weight.(27)

When heated to decomposition, it emits acrid smoke and irritating fumes.

LD_{50} (rat, IP): 1.41 g/kg(28)
LD_{50} (rat, IV): 0.06 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Alginic acid; potassium alginate; sodium alginate; propylene glycol alginate.

18 Comments

Although not included in any pharmacopeias, a specification for calcium alginate is contained in the Food Chemicals Codex (FCC),(29) and has been included in the British Pharmaceutical Codex (BPC);(30) *see* Table I.

Table I: FCC(29) and BPC(30) specifications for calcium alginate.

Test	FCC 1996	BPC 1973
Arsenic	⩽3 ppm	⩽ 3ppm
Ash	12–18%	—
Heavy metals	⩽0.004% (as lead)	—
Iron	—	⩽530 ppm
Lead	⩽10 ppm	⩽10 ppm
Loss on drying	⩽15%	22.00%
Sulfated ash	—	31.0–34.0%
Assay	89.6–104.5%	—

19 Specific References

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21 Authors

CG Cable.

22 Date of Revision

22 August 2005.

Calcium Carbonate

1 Nonproprietary Names

BP: Calcium carbonate
JP: Precipitated calcium carbonate
PhEur: Calcii carbonas
USP: Calcium carbonate

2 Synonyms

Calcium carbonate (1 : 1); carbonic acid calcium salt 1:1; creta preparada; *Destab*; E170; *MagGran CC*; *Micromite*; *Pharma-Carb*; precipitated carbonate of lime; precipitated chalk; *Vivapress Ca*; *Witcarb*.

3 Chemical Name and CAS Registry Number

Carbonic acid, calcium salt (1 : 1) [471-34-1]

4 Empirical Formula and Molecular Weight

$CaCO_3$ 100.09

5 Structural Formula

$CaCO_3$

6 Functional Category

Buffering agent; coating agent; opacifier; tablet and capsule diluent; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Calcium carbonate, employed as a pharmaceutical excipient, is mainly used in solid-dosage forms as a diluent.^(1–6) It is also used as a base for medicated dental preparations, as a buffering agent, and as a dissolution aid in dispersible tablets. Calcium carbonate is used as a bulking agent in tablet sugar-coating processes and as an opacifier in tablet film-coating.

Calcium carbonate is also used as a food additive and therapeutically as an antacid and calcium supplement.

8 Description

Calcium carbonate occurs as an odorless and tasteless white powder or crystals.

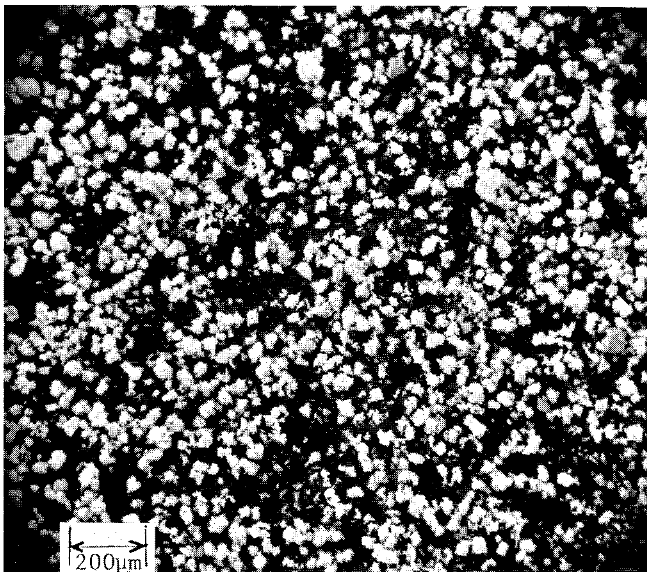
9 Pharmacopeial Specifications

See Table I.

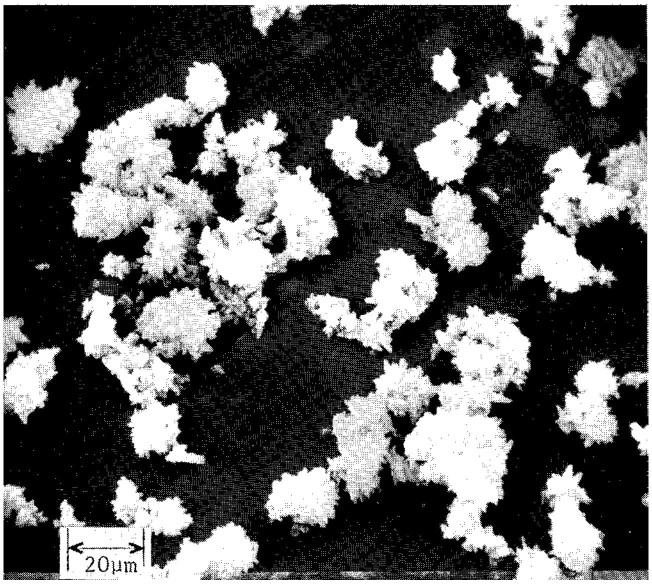
Table I: Pharmacopeial specifications for calcium carbonate.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	—	+	—
Loss on drying	⩽1.0%	⩽2.0%	⩽2.0%
Substances insoluble in acetic acid	⩽0.2%	⩽0.2%	⩽0.2%
Fluoride	—	—	⩽0.005%
Arsenic	⩽5 ppm	⩽4 ppm	⩽3 ppm
Barium	+	+	+
Chlorides	—	⩽330 ppm	—
Lead	—	—	⩽3 ppm
Iron	—	⩽200 ppm	⩽0.1%
Heavy metals	⩽20 ppm	⩽20 ppm	⩽0.002%
Magnesium and alkali (metals) salts	⩽0.5%	⩽1.5%	⩽1.0%
Sulfates	—	⩽0.25%	—
Mercury	—	—	⩽0.5 μg/g
Organic volatile impurities	—	—	+
Assay (dried basis)	⩾ 98.5%	98.5%–100.5%	98.0%–100.5%

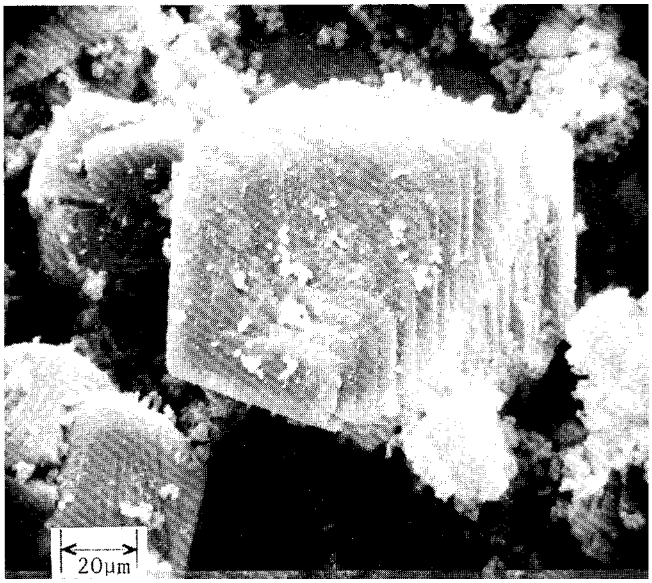
SEM: 1
Excipient: Calcium carbonate
Manufacturer: Whittaker, Clark & Daniels
Lot No.: 15A-3
Magnification: 600×
Voltage: 20 kV



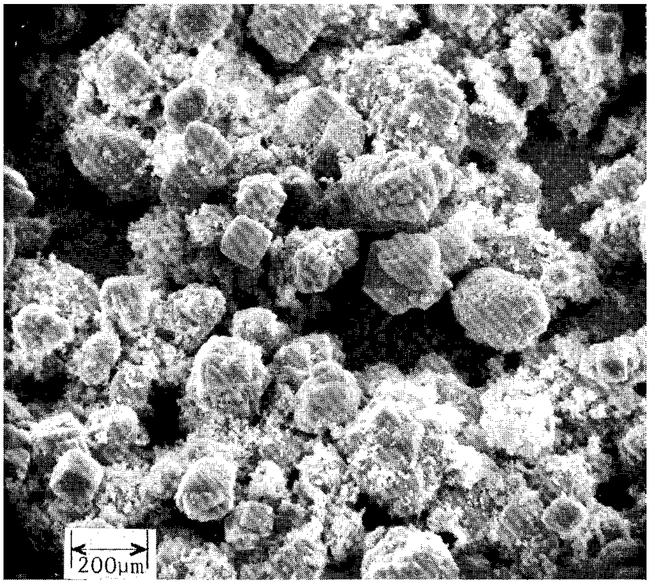
SEM: 2
Excipient: Calcium carbonate
Manufacturer: Whittaker, Clark & Daniels
Lot No.: 15A-3
Magnification: 2400×
Voltage: 20 kV



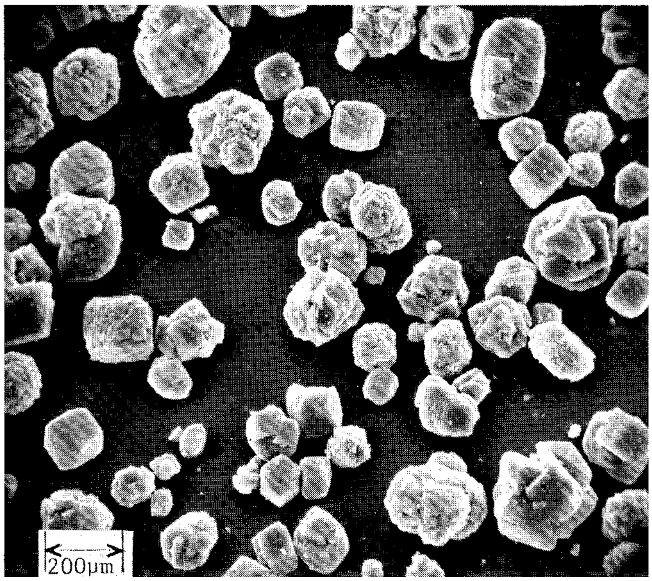
SEM: 4
Excipient: Calcium carbonate
Manufacturer: Whittaker, Clark & Daniels
Lot No.: 15A-4
Magnification: 2400×
Voltage: 20 kV



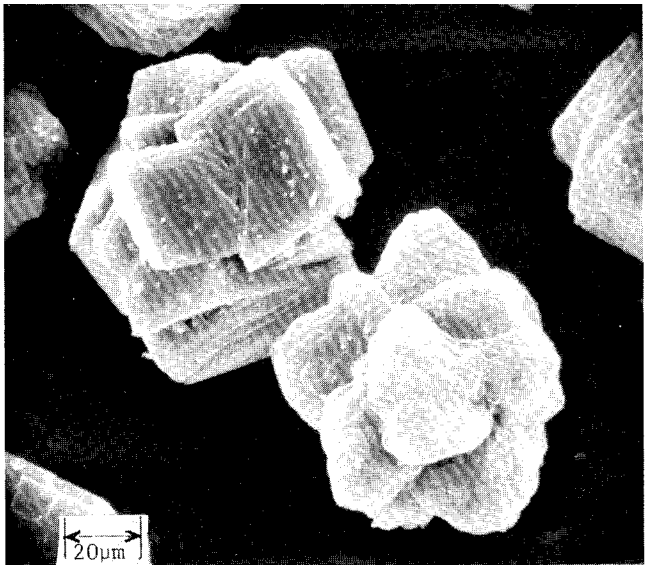
SEM: 3
Excipient: Calcium carbonate
Manufacturer: Whittaker, Clark & Daniels
Lot No.: 15A-4
Magnification: 600×
Voltage: 20 kV



SEM: 5
Excipient: Calcium carbonate
Manufacturer: Whittaker, Clark & Daniels
Lot No.: 15A-2
Magnification: 600×
Voltage: 20 kV



SEM: 6
Excipient: Calcium carbonate
Manufacturer: Whittaker, Clark & Daniels
Lot No.: 15A-2
Magnification: 2400×
Voltage: 20 kV



10 Typical Properties

Acidity/alkalinity: pH = 9.0 (10% w/v aqueous dispersion)
Density (bulk): 0.8 g/cm^3
Density (tapped): 1.2 g/cm^3
Flowability: cohesive.
Hardness (Mohs): 3.0 for *Millicarb*.
Melting point: decomposes at 825°C.
Moisture content: *see* Figure 1.
Particle size: *see* Figure 2.
Refractive index: 1.59
Solubility: practically insoluble in ethanol (95%) and water. Solubility in water is increased by the presence of ammonium salts or carbon dioxide. The presence of alkali hydroxides reduces solubility.
Specific gravity: 2.7
Specific surface area: 6.21–6.47 m^2/g

11 Stability and Storage Conditions

Calcium carbonate is stable and should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatible with acids and ammonium salts (*see also* Sections 10 and 18).

13 Method of Manufacture

Calcium carbonate is prepared by double decomposition of calcium chloride and sodium bicarbonate in aqueous solution. Density and fineness are governed by the concentrations of the solutions. Calcium carbonate is also obtained from the naturally occurring minerals aragonite, calcite, and vaterite.

14 Safety

Calcium carbonate is mainly used in oral pharmaceutical formulations and is generally regarded as a nontoxic material. However, calcium carbonate administered orally may cause constipation and flatulence. Consumption of large quantities (4–60 g daily) may also result in hypercalcemia or renal impairment.(7) Therapeutically, oral doses of up to about 1.5 g are employed as an antacid. In the treatment of hyperphosphatemia in patients with chronic renal failure, oral daily doses of 2.5–17 g have been used. Calcium carbonate may interfere with the absorption of other drugs from the gastrointestinal tract if administered concomitantly.

LD$_{50}$ (rat, oral): 6.45 g/kg

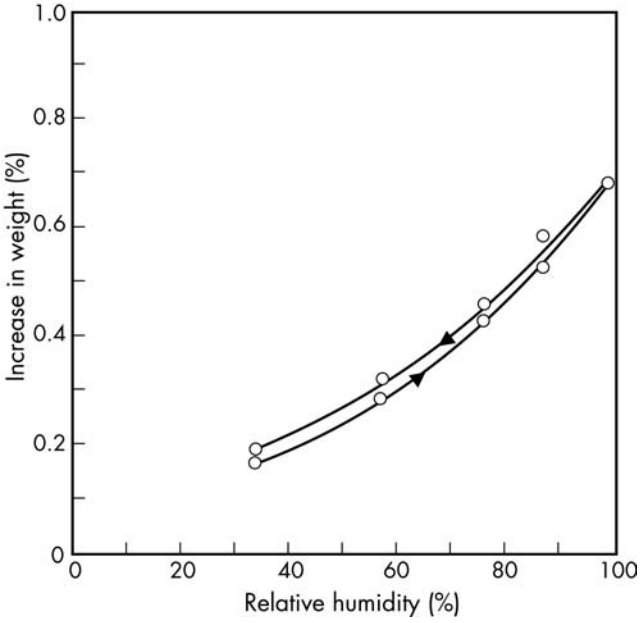


Figure 1: Moisture sorption–desorption isotherm of calcium carbonate.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Calcium carbonate may be irritant to the eyes and on inhalation. Eye protection, gloves, and a dust mask are recommended. Calcium carbonate should be handled in a well-ventilated environment. In the UK, the long-term (8-hour TWA) occupational exposure limit for calcium carbonate is 10 mg/m^3 for total inhalable dust and 4 mg/m^3 for respirable dust.(8)

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets; otic solutions). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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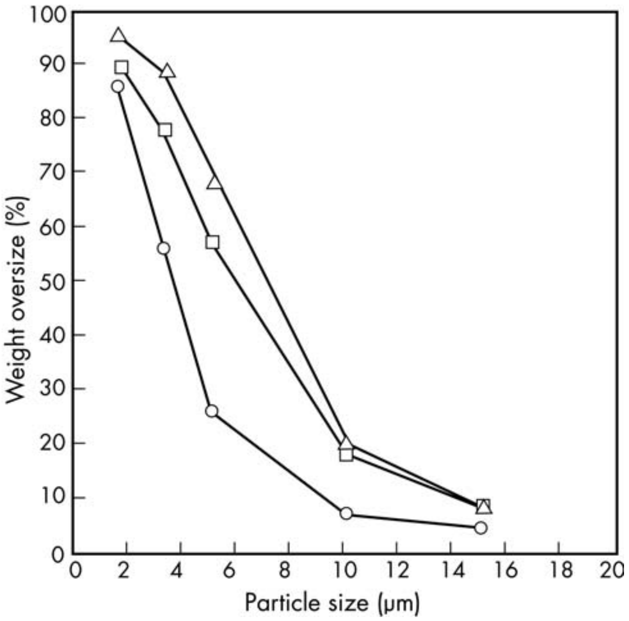

Figure 2: Particle-size distribution of calcium carbonate (*Sturcal*, Rhodia).
○: *Sturcal F*
□: *Sturcal H*
△: *Sturcal L*

18 Comments

When calcium carbonate is used in tablets containing aspirin and related substances, traces of iron may cause discoloration. This may be overcome by inclusion of a suitable chelating agent. Grades with reduced lead levels are commercially available for use in antacids and calcium supplements.

Directly compressible tablet diluents containing calcium carbonate and other excipients are commercially available. Examples of such grades are *Barcroft CS90* (containing 10% starch), *Barcroft CX50* (containing 50% sorbitol), and *Barcroft CZ50* (containing 50% sucrose) available from SPI Pharma. Available from DMV International, are *Cal-Carb 4450 PG* (containing maltodextrin), and *Cal-Carb 4457* and *Cal-Carb 4462* (both containing pregelatinized corn starch).

Two directly compressible grades containing only calcium carbonate are commercially available (*Vivapress Ca 740* and *Vivapress Ca 800*, J. Rettenmaier and Söhne).

A specification for calcium carbonate is contained in the Food Chemicals Codex (FCC).

The EINECS number for calcium carbonate is 207-439-9.

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21 Authors

NA Armstrong.

22 Date of Revision

16 August 2005.

Calcium Phosphate, Dibasic Anhydrous

1 Nonproprietary Names

BP: Anhydrous calcium hydrogen phosphate
JP: Anhydrous dibasic calcium phosphate
PhEur: Calcii hydrogenophosphas anhydricus
USP: Dibasic calcium phosphate

2 Synonyms

A-TAB; calcium monohydrogen phosphate; calcium orthophosphate; *Di-Cafos AN*; dicalcium orthophosphate; E341; *Emcompress Anhydrous*; *Fujicalin*; phosphoric acid calcium salt (1 : 1); secondary calcium phosphate.

3 Chemical Name and CAS Registry Number

Dibasic calcium phosphate [7757-93-9]

4 Empirical Formula and Molecular Weight

$CaHPO_4$ 136.06

5 Structural Formula

$CaHPO_4$

6 Functional Category

Tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Anhydrous dibasic calcium phosphate is used both as an excipient and as a source of calcium in nutritional supplements. It is used particularly in the nutritional/health food sectors. It is also used in pharmaceutical products because of its compaction properties, and the good flow properties of the coarse-grade material.(1–5) The predominant deformation mechanism of anhydrous dibasic calcium phosphate coarse-grade is brittle fracture and this reduces the strain-rate sensitivity of the material, thus allowing easier transition from the laboratory to production scale. However, unlike the dihydrate, anhydrous dibasic calcium phosphate when compacted at higher pressures can exhibit lamination and capping. This phenomenon can be observed when the material represents a substantial proportion of the formulation and is exacerbated by the use of deep concave tooling. This phenomenon also appears to be independent of rate of compaction.

Anhydrous dibasic calcium phosphate is abrasive and a lubricant is required for tableting, for example 1% w/w magnesium stearate or 1% w/w sodium stearyl fumarate.

Two particle-size grades of anhydrous dibasic calcium phosphate are used in the pharmaceutical industry. Milled material is typically used in wet-granulated or roller-compacted formulations. The 'unmilled' or coarse-grade material is typically used in direct-compression formulations.

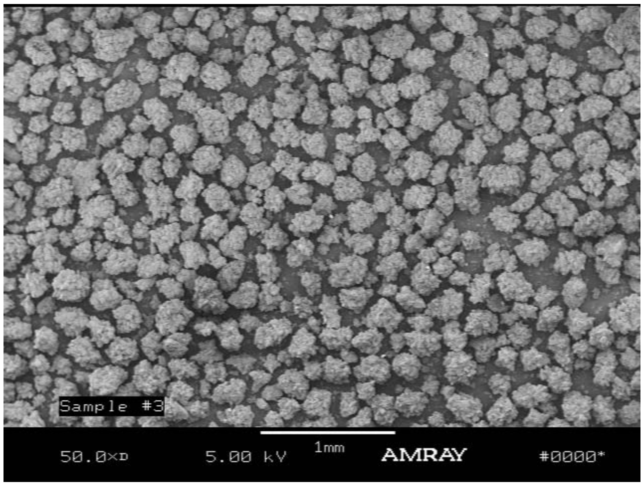
Anhydrous dibasic calcium phosphate is nonhygroscopic and stable at room temperature. It does not hydrate to form the dihydrate.

Anhydrous dibasic calcium phosphate is used in toothpaste and dentifrice formulations for its abrasive properties.

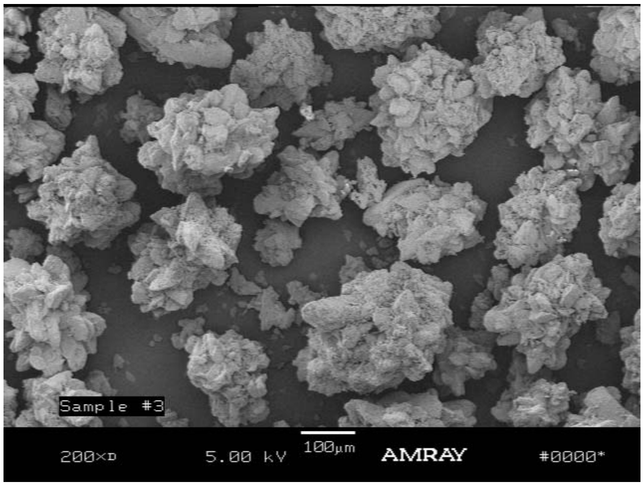
8 Description

Anhydrous dibasic calcium phosphate is a white, odorless, tasteless powder or crystalline solid. It occurs as triclinic crystals.

SEM: 1
Excipient: Emcompress Anhydrous
Manufacturer: JRS Pharma LP
Magnification: 50×
Voltage: 5 kV



SEM: 2
Excipient: Emcompress Anhydrous
Manufacturer: JRS Pharma LP
Magnification: 200×
Voltage: 5 kV



9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for calcium phosphate, dibasic anhydrous.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	+	+	—
Loss on ignition	—	—	6.6–8.5%
Loss on drying	⩽1.0%	⩽2.0%	—
Acid insoluble substance	⩽0.05%	—	⩽0.2%
Heavy metals	⩽31 ppm	⩽40 ppm	⩽0.003%
Chloride	⩽0.248%	⩽330 ppm	⩽0.25%
Fluoride	—	⩽100 ppm	⩽0.005%
Sulfate	⩽0.200%	⩽0.5%	⩽0.5%
Carbonate	+	+	+
Barium	+	+	+
Arsenic	⩽2 ppm	⩽10 ppm	⩽3 μg/g
Organic volatile impurities	—	—	+
Iron	—	⩽400 ppm	—
Assay (dried basis)	⩾98.0%	98.0–101.0%	98.0–105.0%

10 Typical properties

Acidity/alkalinity:
pH = 7.3 (20% slurry);
pH = 5.1 (20% slurry of *A-TAB*);
pH = 6.1–7.2 (5% slurry of *Fujicalin*).
Angle of repose: 32° (for *Fujicalin*)
Density: 2.89 g/cm^3
Density (bulk):
0.78 g/cm^3 for *A-TAB*;
0.45 g/cm^3 for *Fujicalin*.
Density (tapped):
0.82 g/cm^3 for *A-TAB*;
0.46 g/cm^3 for *Fujicalin*.
Melting point: does not melt; decomposes at ≈425°C to form calcium pyrophosphate.
Moisture content: 0.1–0.2%. The anhydrous material contains only surface-adsorbed moisture and cannot be rehydrated to form the dihydrate.
Particle size distribution:
A-TAB: average particle diameter 180 μm;
Encompress Anhydrous: average particle diameter 136 μm;
Fujicalin: average particle diameter 94 μm;
Powder: average particle diameter: 15 μm.
Solubility: practically insoluble in ether, ethanol, and water; soluble in dilute acids.
Specific surface area:
20–30 m^2/g for *A-TAB*;
35 m^2/g for *Fujicalin*.

11 Stability and Storage Conditions

Dibasic calcium phosphate anhydrous is a nonhygroscopic, relatively stable material. Under conditions of high humidity it does not hydrate to form the dihydrate.

The bulk material should be stored in a well-closed container in a dry place.

12 Incompatibilities

Dibasic calcium phosphate should not be used to formulate tetracyline antibiotics.(6)

The surface of milled anhydrous dibasic calcium phosphate is alkaline(2) and consequently it should not be used with drugs that are sensitive to alkaline pH. However, reports(7,8) suggest there are differences in the surface alkalinity/acidity between the milled and unmilled grades of anhydrous dibasic calcium phosphate; the unmilled form has an acidic surface environment. This difference has important implications for drug stability, particularly when reformulating from, e.g. roller compaction to direct compression, when the particle size of the anhydrous dibasic calcium phosphate might be expected to change.

Dibasic calcium phosphate dihydrate has been reported to be incompatible with a number of drugs and excipients and many of these incompatibilities are expected to occur with dibasic calcium phosphate, anhydrous; *see* Calcium phosphate, dibasic dihydrate.

13 Method of Manufacture

Calcium phosphates are usually prepared by reacting very pure phosphoric acid with calcium hydroxide, $Ca(OH)_2$ obtained from limestone, in stoichiometric ratio in aqueous suspension(2) followed by drying at a temperature that will allow the correct hydration state to be achieved. After drying, the coarse-grade material is obtained by means of a classification unit; the fine particle-size material is obtained by milling. Dibasic calcium phosphate, anhydrous, may also be prepared by spray-drying.(9,10)

14 Safety

Dibasic calcium phosphate anhydrous is widely used in oral pharmaceutical products, food products, and toothpastes and is generally regarded as a relatively nontoxic and nonirritant material.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. The fine-milled grades can generate nuisance dusts and the use of a respirator or dust mask may be necessary.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in Europe. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Calcium phosphate, dibasic dihydrate; calcium phosphate, tribasic; calcium sulfate.

18 Comments

Grades of anhydrous dibasic calcium phosphate available for direct compression include *A-TAB* (Rhodia), *Di-Cafos AN* (Chemische Fabrik Budenheim), *Emcompress Anhydrous* (JRS Pharma LP), and *Fujicalin* (Fuji Chemical Industry Co. Ltd.).

The EINECS number for calcium phosphate is 231-837-1.

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21 Authors

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22 Date of Revision

30 August 2005.

Calcium Phosphate, Dibasic Dihydrate

1 Nonproprietary Names

BP: Calcium hydrogen phosphate
JP: Dibasic calcium phosphate
PhEur: Calcii hydrogenophosphas dihydricus
USP: Dibasic calcium phosphate

2 Synonyms

Calcium hydrogen orthophosphate dihydrate; calcium monohydrogen phosphate dihydrate; *Di-Cafos*; dicalcium orthophosphate; *DI-TAB*; E341; *Emcompress*; phosphoric acid calcium salt (1 : 1) dihydrate; secondary calcium phosphate.

3 Chemical Name and CAS Registry Number

Dibasic calcium phosphate dihydrate [7789-77-7]

4 Empirical Formula and Molecular Weight

$CaHPO_4{\cdot}2H_2O$ 172.09

5 Structural Formula

$CaHPO_4{\cdot}2H_2O$

6 Functional Category

Tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Dibasic calcium phosphate dihydrate is widely used in tablet formulations both as an excipient and as a source of calcium and phosphorus in nutritional supplements.(1–8) It is one of the more widely used materials, particularly in the nutritional/health food sectors. It is also used in pharmaceutical products because of its compaction properties, and the good flow properties of the coarse-grade material. The predominant deformation mechanism of dibasic calcium phosphate coarse-grade is brittle fracture and this reduces the strain-rate sensitivity of the material, thus allowing easier transition from the laboratory to production scale. However, dibasic calcium phosphate dihydrate is abrasive and a lubricant is required for tableting, for example about 1% w/w of magnesium stearate or about 1% w/w of sodium stearyl fumarate is commonly used.

Two main particle-size grades of dibasic calcium phosphate dihydrate are used in the pharmaceutical industry. The milled material is typically used in wet-granulated, roller-compacted or slugged formulations. The ‘unmilled’ or coarse-grade material is typically used in direct-compression formulations.

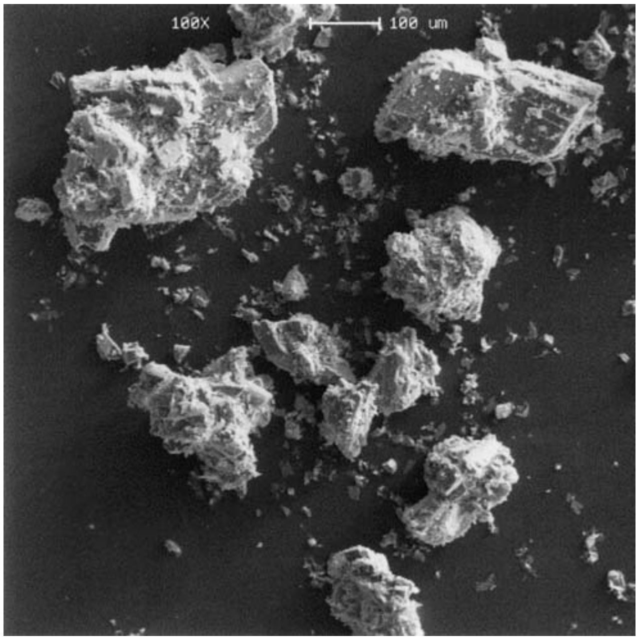
Dibasic calcium phosphate dihydrate is nonhygroscopic and stable at room temperature. However, under certain conditions of temperature and humidity, it can lose water of crystallization below 100°C. This has implications for certain types of packaging and aqueous film coating since the loss of water of crystallization appears to be initiated by high humidity and by implication high moisture vapor concentrations in the vicinity of the dibasic calcium phosphate dihydrate particles.(8)

Dibasic calcium phosphate dihydrate is also used in toothpaste and dentifrice formulations for its abrasive properties.

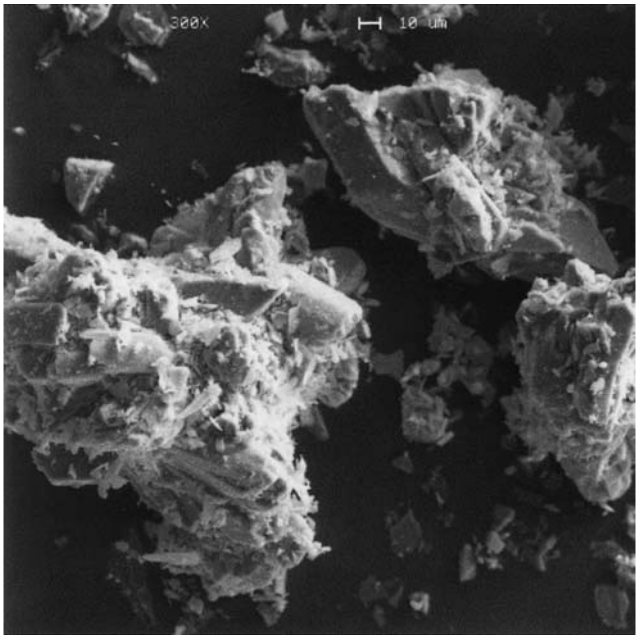
8 Description

Dibasic calcium phosphate dihydrate is a white, odorless, tasteless powder or crystalline solid. It occurs as monoclinic crystals.

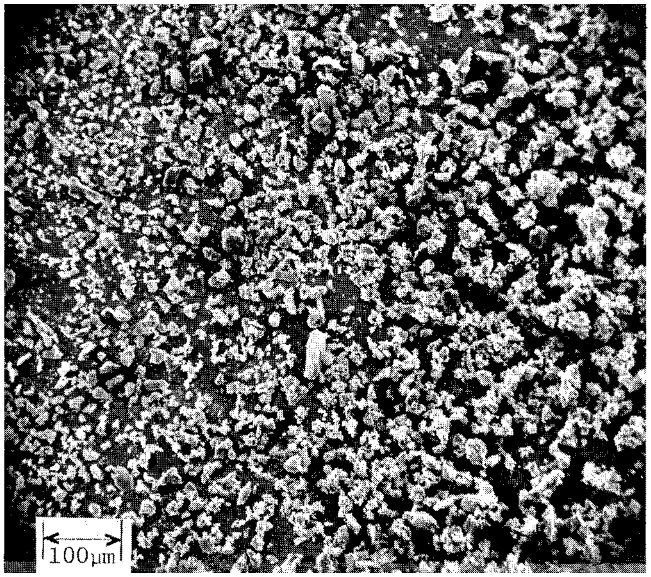
SEM: 1
Excipient: Dibasic calcium phosphate dihydrate, coarse grade
Manufacturer: JRS Pharma LP.
Lot No.: W28C
Magnification: 100×



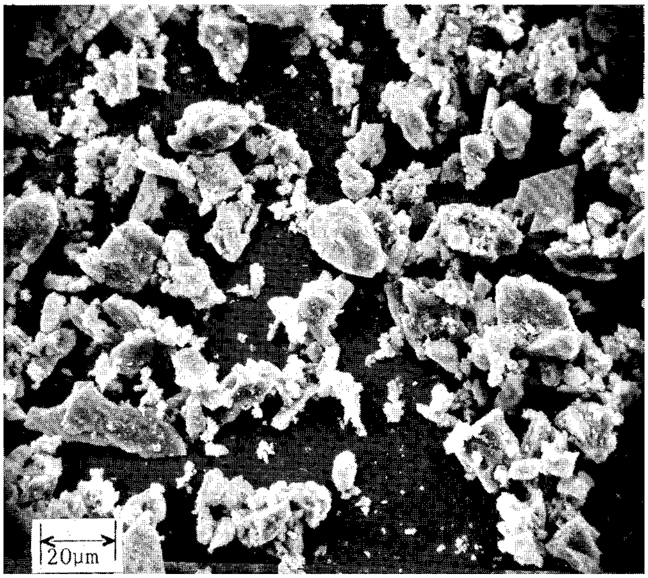
SEM: 2
Excipient: Dibasic calcium phosphate dihydrate, coarse grade
Manufacturer: JRS Pharma LP.
Lot No.: W28C
Magnification: 300×



SEM: 3
Excipient: Dibasic calcium phosphate dihydrate
Manufacturer: Rhodia.
Lot No.: 16A-1 (89)
Magnification: 120×



SEM: 4
Excipient: Dibasic calcium phosphate dihydrate, coarse grade
Manufacturer: Rhodia.
Lot No.: 16A-1 (89)
Magnification: 600×



9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for calcium phosphate, dibasic dihydrate.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	+	+	—
Loss on ignition	—	—	24.5–26.5%
Loss on drying	19.5–22.0%	—	—
Acid insoluble substances	⩽0.05%	—	⩽0.2%
Heavy metals	⩽31 ppm	⩽40 ppm	⩽0.003%
Chloride	⩽0.248%	⩽330 ppm	⩽0.25%
Fluoride	—	⩽100 ppm	⩽0.005%
Sulfate	⩽0.160%	⩽0.5%	⩽0.5%
Carbonate	+	+	+
Barium	+	+	+
Arsenic	⩽2 ppm	⩽10 ppm	⩽3 μg/g
Organic volatile impurities	—	—	+
Iron	—	⩽400 ppm	—
Assay	⩾98.0%	98.0–105.0%	98.0–105.0%

10 Typical Properties

Acidity/alkalinity: pH = 7.4 (20% slurry of *DI-TAB*)
Angle of repose: 28.3° for *Emcompress.*(9)
Density (bulk): 0.915 g/cm^3
Density (tapped): 1.17 g/cm^3
Density (true): 2.389 g/cm^3

Flowability:
27.3 g/s for *DI-TAB*;
11.4 g/s for *Emcompress*.(9)
Melting point: dehydrates below 100°C.
Moisture content: dibasic calcium phosphate dihydrate contains two molecules of water of crystallization, which can be lost at temperatures well below 100°C.
Particle size distribution: *DI-TAB*: average particle diameter 180 μm
Fine powder: average particle diameter 9 μm
Solubility: practically insoluble in ethanol, ether, and water; soluble in dilute acids.
Specific surface area: 0.44–0.46 m^2/g for *Emcompress*

11 Stability and Storage Conditions

Dibasic calcium phosphate dihydrate is a nonhygroscopic, relatively stable material. However, under certain conditions the dihydrate can lose water of crystallization. This has implications for both storage of the bulk material and coating and packaging of tablets containing dibasic calcium phosphate dihydrate.

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Dibasic calcium phosphate dihydrate should not be used to formulate tetracycline antibiotics.(10) Dibasic calcium phosphate dihydrate has been reported to be incompatible with indomethacin,(11) aspirin,(12) aspartame,(13) ampicillin,(14) cephalexin,(15) and erythromycin.(16) The surface of dibasic calcium phosphate dihydrate is alkaline(16) and consequently it should not be used with drugs that are sensitive to alkaline pH.

13 Method of Manufacture

Calcium phosphates are usually manufactured by reacting very pure phosphoric acid with calcium hydroxide, $Ca(OH)_2$ obtained from limestone, in stoichiometric ratio in aqueous suspension followed by drying at a temperature that will allow the correct hydration state to be achieved. After drying, the coarse-grade material is obtained by means of a classification unit; the fine particle-size material is obtained by milling.

14 Safety

Dibasic calcium phosphate dihydrate is widely used in oral pharmaceutical products, food products, and toothpastes and is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may cause abdominal discomfort.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. The fine-milled grades can generate nuisance dusts and the use of a respirator or dust mask may be necessary.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in Europe. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Calcium phosphate, dibasic anhydrous; calcium phosphate, tribasic.

18 Comments

Grades of dibasic calcium phosphate dihydrate available for direct compression include *Calstar* (FMC Biopolymer), *Di-Cafos* (Chemische Fabrik Budenheim), *DI-TAB* (Rhodia), and *Emcompress* (JRS Pharma LP).

Accelerated stability studies carried out at elevated temperatures on formulations containing significant proportions of dibasic calcium phosphate dihydrate can give erroneous results owing to irreversible dehydration of the dihydrate to the anhydrous form. Depending on the type of packaging and whether or not the tablet is coated, the phenomenon can be observed at temperatures as low as 40°C after 6 weeks of storage. As the amount of dibasic calcium phosphate dihydrate in the tablet is reduced, the effect is less easy to observe.

The EINECS number for calcium phosphate is 231-837-1.

19 Specific References

1 Lausier JM, Chiang C-W, Zompa HA, Rhodes CT. Aging of tablets made with dibasic calcium phosphate dihydrate as matrix. *J Pharm Sci* 1977; **66**(11): 1636–1637.
2 Carstensen JT, Ertell C. Physical and chemical properties of calcium phosphates for solid state pharmaceutical formulations. *Drug Dev Ind Pharm* 1990; **16**(7): 1121–1133.
3 Bryan JW, McCallister JD. Matrix forming capabilities of three calcium diluents. *Drug Dev Ind Pharm* 1992; **18**(19): 2029–2047.
4 Schmidt PC, Herzog R. Calcium phosphates in pharmaceutical tableting I: physico-pharmaceutical properties. *Pharm World Sci* 1993; **15**(3): 105–115.
5 Schmidt PC, Herzog R. Calcium phosphates in pharmaceutical tableting II: comparison of tableting properties. *Pharm World Sci* 1993; **15**(3): 116–122.
6 Landín M, Martínez-Pacheco R, Gómez-Amoza JL, *et al.* The effect of country of origin on the properties of dicalcium phosphate dihydrate powder. *Int J Pharm* 1994; **103**: 9–18.
7 Landín M, Martínez-Pacheco R, Gómez-Amoza JL, *et al.* Dicalcium phosphate dihydrate for direct compression: characterization and intermanufacturer variability. *Int J Pharm* 1994; **109**: 1–8.
8 Landín M, Rowe RC, York P. Structural changes during the dehydration of dicalcium phosphate dihydrate. *Eur J Pharm Sci* 1994; **2**: 245–252.
9 Çelik M, Okutgen E. A feasibility study for the development of a prospective compaction functionality test and the establishment of a compaction data bank. *Drug Dev Ind Pharm* 1993; **19**(17–18): 2309–2334.
10 Weiner M, Bernstein IL. *Adverse Reactions to Drug Formulation Agents: A Handbook of Excipients*. New York: Marcel Dekker, 1989: 93–94.
11 Eerikäinen S, Yliruusi J, Laakso R. The behaviour of the sodium salt of indomethacin in the cores of film-coated granules containing various fillers. *Int J Pharm* 1991; **71**: 201–211.
12 Landín M, Perez-Marcos B, Casalderrey M, *et al.* Chemical stability of acetyl salicylic acid in tablets prepared with different commercial brands of dicalcium phosphate dihydrate. *Int J Pharm* 1994; **107**: 247–249.

13 El-Shattawy HH, Peck GE, Kildsig DO. Aspartame direct compression excipients: preformulation stability screening using differential scanning calorimetry. *Drug Dev Ind Pharm* 1981; **7**(5): 605–619.

14 El-Shattaway HH. Ampicillin direct compression excipients: preformulation stability screening using differential scanning calorimetry. *Drug Dev Ind Pharm* 1982; **8**(6): 819–831.

15 El-Shattaway HH, Kildsig DO, Peck GE. Cephalexin I direct compression excipients: preformulation stability screening using differential scanning calorimetry. *Drug Dev Ind Pharm* 1982; **8**(6): 897–909.

16 El-Shattaway HH, Kildsig DO, Peck GE. Erythromycin direct compression excipients: preformulation stability screening using differential scanning calorimetry. *Drug Dev Ind Pharm* 1982; **8**(6): 937–947.

20 General References

Green CE, Makhija RG, Carstensen JT. R-P trials calcium excipient. *Manuf Chem* 1996; **67**(8): 55, 57.

Rhodia. Technical literature: *Calcium phosphate excipients*, 1999.

21 Authors

RC Moreton.

22 Date of Revision

22 August 2005.

Calcium Phosphate, Tribasic

1 Nonproprietary Names

BP: Calcium phosphate
PhEur: Tricalcii phosphas
USPNF: Tribasic calcium phosphate

2 Synonyms

Calcium orthophosphate; E341; hydroxylapatite; phosphoric acid calcium salt (2 : 3); precipitated calcium phosphate; tertiary calcium phosphate; *Tri-Cafos*; tricalcium diorthophosphate; tricalcium orthophosphate; tricalcium phosphate; *TRI-CAL WG*; *TRI-TAB*.

3 Chemical Name and CAS Registry Number

Tribasic calcium phosphate is not a clearly defined chemical entity but is a mixture of calcium phosphates. Several chemical names, CAS Registry Numbers, and molecular formulas have therefore been used to describe this material. Those most frequently cited are shown below.

Calcium hydroxide phosphate [12167-74-7]
Tricalcium orthophosphate [7758-87-4]

See also Sections 4 and 8.

4 Empirical Formula and Molecular Weight

$Ca_3(PO_4)_2$	310.20
$Ca_5(OH)(PO_4)_3$	502.32

5 Structural Formula

See Sections 3 and 4.

6 Functional Category

Anticaking agent; buffer; dietary supplement; glidant; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Tribasic calcium phosphate is widely used as a capsule diluent and tablet filler/binder in either direct-compression or wet-granulation processes. The primary bonding mechanism in compaction is plastic deformation. As with dibasic calcium phosphate, a lubricant and a disintegrant should usually be incorporated in capsule or tablet formulations that include tribasic calcium phosphate. In some cases tribasic calcium phosphate has been used as a disintegrant.(1) It is most widely used in vitamin and mineral preparations(2) as a filler and as a binder. It is a source of both calcium and phosphorus, the two main osteogenic minerals for bone health. The bioavailability of the calcium is well known to be improved by the presence of cholecalciferol. Recent research reports that combinations of tribasic calcium phosphate and vitamin D3 are a cost-effective advance in bone fracture prevention.(3)

In food applications, tribasic calcium phosphate powder is widely used as an anticaking agent. *See* Section 18.

See also Calcium phosphate, dibasic dihydrate.

8 Description

The PhEur 2005 states that tribasic calcium phosphate consists of a mixture of calcium phosphates. It contains not less than 35.0% and not more than the equivalent of 40.0% of calcium. The USPNF 23 specifies that tribasic calcium phosphate consists of variable mixtures of calcium phosphates having the approximate composition $10CaO{\cdot}3P_2O_5{\cdot}H_2O$. This corresponds to a molecular formula of $Ca_5(OH)(PO_4)_3$ or $Ca_{10}(OH)_2(PO_4)_6$.

Tribasic calcium phosphate is a white, odorless and tasteless powder.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for tribasic calcium phosphate.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Loss on ignition	⩽8.0%	⩽8.0%
Water-soluble substances	—	⩽0.5%
Acid-insoluble substances	⩽0.2%	⩽0.2%
Carbonate	—	+
Chloride	⩽0.15%	⩽0.14%
Fluoride	⩽75 ppm	⩽0.0075%
Nitrate	—	+
Sulfate	⩽0.5%	⩽0.8%
Arsenic	⩽4 ppm	⩽3 ppm
Barium	—	+
Iron	⩽400 ppm	—
Dibasic salt and calcium oxide	—	+
Heavy metals	⩽30 ppm	⩽0.003%
Assay (as Ca)	35.0–40.0%	34.0–40.0%

10 Typical Properties

Acidity/alkalinity: pH = 6.8 (20% slurry in water)

Density: 3.14 g/cm^3

Density (bulk):

0.3–0.4 g/cm^3 for powder form;
0.80 g/cm^3 for granular *TRI-TAB*.(4)

Density (tapped): 0.95 g/cm^3 for granular *TRI-TAB*.(4)

Flowability: 25.0 g/s for granular *TRI-TAB*(4)

Melting point: 1670°C

Moisture content: slightly hygroscopic. A well-defined crystalline hydrate is not formed although surface moisture may be picked up or contained within small pores in the crystal structure. At relative humidities between about 15% and 65%, the equilibrium moisture content at 25°C is about 2.0%. At relative humidities above about 75%, tribasic calcium phosphate may absorb small amounts of moisture.

Particle size distribution: Tribasic calcium phosphate powder: typical particle diameter 5–10 μm; 98% of particles <44 μm.

TRI-CAL WG: average particle diameter 180 μm; 99% of particles <420 μm, 46% <149 μm, and 15% <44 μm in size.

TRI-TAB: average particle diameter 350 μm; 97% of particles <420 μm, and 2% <149 μm.

Solubility: soluble in dilute mineral acids; very slightly soluble in water; practically insoluble in acetic acid and alcohols.

Specific surface area: 70–80 m^2/g(4)

11 Stability and Storage Conditions

Tribasic calcium phosphate is a chemically stable material, and is also not liable to cake during storage.

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

All calcium salts are incompatible with tetracycline antibiotics. Tribasic calcium phosphate is incompatible with tocopheryl acetate (but not tocopheryl succinate). Tribasic calcium phosphate may form sparingly soluble phosphates with hormones.

13 Method of Manufacture

Tribasic calcium phosphate occurs naturally as the minerals hydroxylapatite, voelicherite, and whitlockite. Commercially, it is prepared by treating phosphate-containing rock with sulfuric acid. Tribasic calcium phosphate powder is then precipitated by the addition of calcium hydroxide. Tribasic calcium phosphate is alternatively prepared by treating calcium hydroxide from limestone with purified phosphoric acid. It may also be obtained from calcined animal bones.(5) Some tribasic calcium phosphate products may be prepared in coarser, directly compressible forms by granulating the powder using roller compaction or spray drying.

14 Safety

Tribasic calcium phosphate is widely used in oral pharmaceutical formulations and food products and is generally regarded as nontoxic and nonirritant at the levels employed as a pharmaceutical excipient.

Ingestion or inhalation of excessive quantities may result in the deposition of tribasic calcium phosphate crystals in tissues. These crystals may lead to inflammation and cause tissue lesions in the areas of deposition.

Oral ingestion of very large quantities of tribasic calcium phosphate may cause abdominal discomfort such as nausea and vomiting.

No teratogenic effects were found in chicken embryos exposed to a dose of 2.5 mg of tribasic calcium phosphate.(6)

LD_{50} (rat, oral): >1 g/kg(4)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Handle in a well-ventilated environment since dust inhalation may be an irritant. For processes generating large amounts of dust, the use of a respirator is recommended.

16 Regulatory Acceptance

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Calcium phosphate, dibasic anhydrous; calcium phosphate, dibasic dihydrate.

18 Comments

One gram of tribasic calcium phosphate represents approximately 10.9 mmol of calcium and 6.4 mmol of phosphate; 38% calcium and 17.3% phosphorus by weight.(4) Tribasic calcium phosphate provides a higher calcium load than dibasic calcium phosphate and a higher Ca/P ratio. Granular and fine powder forms of tribasic calcium phosphate are available from various manufacturers.

A specification for calcium phosphate tribasic is contained in the Food Chemicals Codex (FCC).

The EINECS number for calcium phosphate is 231-837-1.

19 Specific References

1 Delonca H, Puech A, Segura G, Youakim J. Effect of excipients and storage conditions on drug stability I: acetylsalicylic acid-based tablets [in French]. *J Pharm Belg* 1969; **24**: 243–252.
2 Magid L. Stable multivitamin tablets containing tricalcium phosphate. United States Patent No. 3,564,097; 1971.
3 Lilliu H, Chapuy MC, Meunier PJ, *et al*. Calcium-vitamin D3 supplementation is cost-effective in hip fractures prevention. *Muturitas* 2003; **44**(4): 299–305.
4 Rhodia. Technical literature: *Calcium phosphate pharmaceutical ingredients*, 1995.
5 Magami A. Basic pentacalcium triphosphate production. Japanese Patent 56 022 614; 1981.
6 Verrett MJ, Scott WF, Reynaldo EF, *et al*. Toxicity and teratogenicity of food additive chemicals in the developing chicken embryo. *Toxicol Appl Pharmacol* 1980; **56**: 265–273.

20 General References

Bryan JW, McCallister JD. Matrix forming capabilities of three calcium diluents. *Drug Dev Ind Pharm* 1992; **18**: 2029–2047.

Chowhan ZT, Amaro AA. The effect of low- and high-humidity aging on the hardness, disintegration time and dissolution rate of tribasic calcium phosphate-based tablets. *Drug Dev Ind Pharm* 1979; **5**: 545–562.

Fischer E. Calcium phosphate as a pharmaceutical excipient. *Manuf Chem* 1992; **64**(6): 25–27.

Kutty TRN. Thermal decomposition of hydroxylapatite. *Indian J Chem* 1973; **11**: 695–697.

Molokhia AM, Moustafa MA, Gouda MW. Effect of storage conditions on the hardness, disintegration and drug release from some tablet bases. *Drug Dev Ind Pharm* 1982; **8**: 283–292.

Pontier C, Viana M. Energetic yields in apatitic calcium phosphate compression: influence of the Ca/P molar ratio. *Polymer International* 2003; **52**(4): 625–628.

Schmidt PC, Herzog R. Calcium phosphates in pharmaceutical tableting 1: physico-pharmaceutical properties. *Pharm World Sci* 1993; **15**(3): 105–115.

Schmidt PC, Herzog R. Calcium phosphates in pharmaceutical tableting 2: comparison of tableting properties. *Pharm World Sci* 1993; **15**(3): 116–122.

21 Authors

V King, L Hendricks, W Camarco.

22 Date of Revision

15 August 2005.

Calcium Stearate

1 Nonproprietary Names

BP: Calcium stearate
JP: Calcium stearate
PhEur: Calcii stearas
USPNF: Calcium stearate

2 Synonyms

Calcium distearate; *HyQual*; stearic acid, calcium salt; calcium octadecanoate; octadecanoic acid, calcium salt.

3 Chemical Name and CAS Registry Number

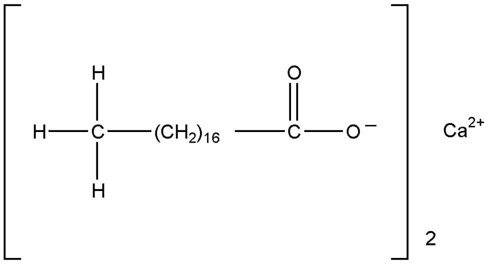
Octadecanoic acid calcium salt [1592-23-0]

4 Empirical Formula and Molecular Weight

$C_{36}H_{70}CaO_4$ 607.03 (for pure material)

The PhEur 2005 describes calcium stearate as a mixture of calcium salts of different fatty acids consisting mainly of stearic acid [$(C_{17}H_{35}COO)_2Ca$] and palmitic acid [$(C_{15}H_{31}COO)_2Ca$] with minor proportions of other fatty acids. It contains the equivalent of 9.0–10.5% of calcium oxide.

5 Structural Formula



$$\left[\mathrm{H}-\overset{\mathrm{H}}{\underset{\mathrm{H}}{\overset{|}{\underset{|}{\mathrm{C}}}}}-(\mathrm{CH_2})_{16}-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\mathrm{O}^- \right]_2 \mathrm{Ca}^{2+}$$

6 Functional Category

Tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

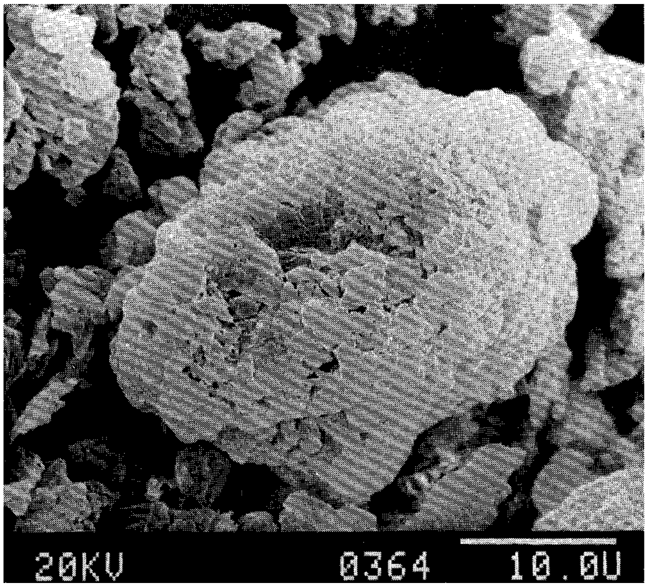
Calcium stearate is primarily used in pharmaceutical formulations as a lubricant in tablet and capsule manufacture at concentrations up to 1.0% w/w. Although it has good antiadherent and lubricant properties, calcium stearate has poor glidant properties.

Calcium stearate is also employed as an emulsifier, stabilizing agent, and suspending agent, and is also used in cosmetics and food products.

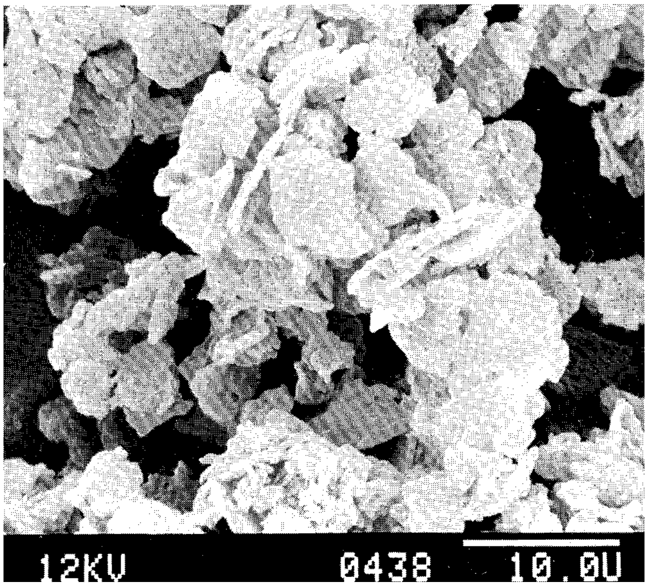
8 Description

Calcium stearate occurs as a fine, white to yellowish-white, bulky powder having a slight, characteristic odor. It is unctuous and free from grittiness.

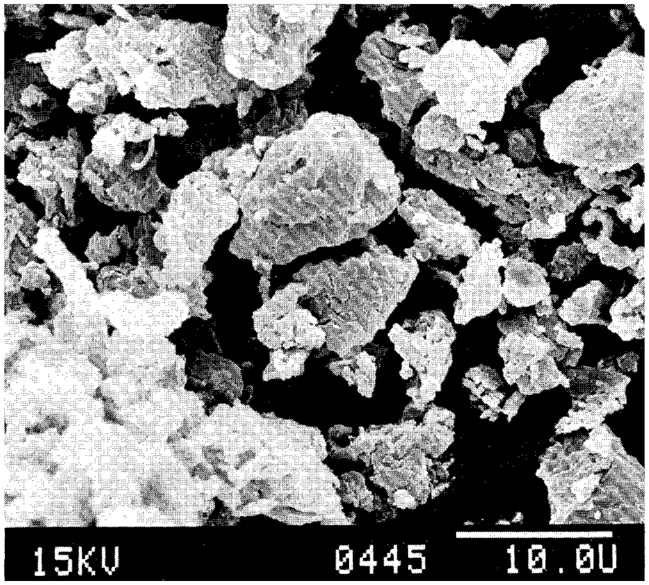
SEM: 1
Excipient: Calcium stearate (Standard)
Manufacturer: Durham Chemicals
Lot No.: 0364
Voltage: 20 kV



SEM: 2
Excipient: Calcium stearate (Precipitated)
Manufacturer: Witco Corporation
Lot No.: 0438
Voltage: 12 kV



SEM: 3
Excipient: Calcium stearate (Fused)
Manufacturer: Witco Corporation
Voltage: 15 kV



9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for calcium stearate.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	+	+	—
Microbial limit	—	10^3/g	—
Acidity or alkalinity	—	+	—
Loss on drying	≤4.0%	≤6.0%	≤4.0%
Arsenic	≤2 ppm	—	—
Heavy metals	≤20 ppm	—	≤10 µg/g
Chlorides	—	≤0.1%	—
Sulfates	—	≤0.3%	—
Cadmium	—	≤3 ppm	—
Lead	—	≤10 ppm	—
Nickel	—	≤5 ppm	—
Organic volatile impurities	—	—	+
Assay (as CaO)	—	—	9.0–10.5%
Assay (as Ca)	6.4–7.1%	6.4–7.4%	—

10 Typical Properties

Acid value: 191–203
Ash: 9.9–10.3%
Chloride: <200 ppm
Density (bulk and tapped): *see* Table II.
Density (true): 1.064–1.096 g/cm^3
Flowability: 21.2–22.6% (Carr compressibility index)
Free fatty acid: 0.3–0.5%
Melting point: 149–160°C
Moisture content: 2.96%
Particle size distribution: 1.7–60 µm; 100% through a 73.7 µm (#200 mesh); 99.5% through a 44.5 µm (#325 mesh).

Table II: Density (bulk and tapped) of calcium stearate.

	Bulk density (g/cm^3)	Tapped density (g/cm^3)
Durham Chemicals		
Standard	—	0.26
A	—	0.45
AM	—	0.33
Witco Corporation		
EA	0.21	0.27
Fused	0.38	0.48
Precipitated	0.16	0.20

Shear strength: 14.71 MPa
Solubility: practically insoluble or insoluble in ethanol (95%), ether, chloroform, acetone and water. Slightly soluble in hot alcohol, and hot vegetable and mineral oils. Soluble in hot pyridine.
Specific surface area: 4.73–8.03 m^2/g
Sulfate: <0.25%

11 Stability and Storage Conditions

Calcium stearate is stable and should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

—

13 Method of Manufacture

Calcium stearate is prepared by the reaction of calcium chloride with a mixture of the sodium salts of stearic and palmitic acids. The calcium stearate formed is collected and washed with water to remove any sodium chloride.

14 Safety

Calcium stearate is used in oral pharmaceutical formulations and is generally regarded as a relatively nontoxic and nonirritant material.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Calcium stearate should be used in a well-ventilated environment; eye protection, gloves, and a respirator are recommended.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Magnesium stearate; stearic acid; zinc stearate.

18 Comments

Calcium stearate exhibits interesting properties when heated; softening between 120–130°C, and exhibiting a viscous consistency at approximately 160°C. At approximately 100°C, it loses about 3% of its weight, corresponding to one mole of water of crystallization. The crystalline structure changes at this point, leading to the collapse of the crystal lattice at a temperature of about 125°C.(1)

See Magnesium stearate for further information and references.

A specification for calcium stearate is contained in the Food Chemicals Codex (FCC).

The EINECS number for calcium stearate is 216-472-8.

19 Specific References

1 SpecialChem (2005). Metallic stearates center. http://www.specialchem4polymers.com/tc/metallic-stearates/index.aspx?id-2404 (accessed 9 August 2005).

20 General References

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Phadke DS, Sack MJ. Evaluation of batch-to-batch and manufacturer-to-manufacturer variability in the physical and lubricant properties of calcium stearate. *Pharm Technol* 1996; **20**(Mar): 126–140.

21 Authors

LV Allen.

22 Date of Revision

9 August 2005.

Calcium Sulfate

1 Nonproprietary Names

BP: Calcium sulphate dihydrate
PhEur: Calcii sulfas dihydricus
USPNF: Calcium sulfate

2 Synonyms

Calcium sulfate anhydrous: anhydrite; anhydrous gypsum; anhydrous sulfate of lime; *Destab*; *Drierite*; E516; karstenite; muriacite; *Snow White*.

Calcium sulfate dihydrate: alabaster; *Cal-Tab*; *Compactrol*; *Destab*; E516; gypsum; light spar; mineral white; native calcium sulfate; precipitated calcium sulfate; satinite; satin spar; selenite; terra alba; *USG Terra Alba*.

3 Chemical Name and CAS Registry Number

Calcium sulfate	[7778-18-9]
Calcium sulfate dihydrate	[10101-41-4]

4 Empirical Formula and Molecular Weight

$CaSO_4$	136.14
$CaSO_4{\cdot}2H_2O$	172.17

5 Structural Formula

$CaSO_4$
$CaSO_4{\cdot}2H_2O$

6 Functional Category

Tablet and capsule diluent. The anhydrous form is used as a desiccant.

7 Applications in Pharmaceutical Formulation or Technology

Calcium sulfate dihydrate is used in the formulation of tablets and capsules. In granular form it has good compaction properties and moderate disintegration properties.(1,2)

Calcium sulfate hemihydrate (*see* Section 17), is used in the preparation of plaster of Paris bandage, which is used for the immobilization of limbs and fractures; it should not be used in the formulation of tablets or capsules.

Anhydrous calcium sulfate is hygroscopic and uptake of water can cause the tablets to become very hard and to fail to disintegrate on storage. It is not recommended for the formulation of tablets, capsules, or powders for oral administration.

Therapeutically, calcium sulfate is used in dental and craniofacial surgical procedures.(3,4)

8 Description

A white or off-white, fine, odorless, and tasteless powder or granules.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for calcium sulfate.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Acidity or alkalinity	+	—
Arsenic	⩽10 ppm	—
Chlorides	⩽300 ppm	—
Heavy metals	⩽20 ppm	⩽0.001%
Iron	⩽100 ppm	⩽0.01%
Loss on drying		
Anhydrous	—	⩽1.5%
Dihydrate	—	19.0–23.0%
Loss on ignition	18.0–22.0%	—
Assay	98.0–102.0%	98.0–101.0%

10 Typical properties

Acidity/alkalinity:
pH = 7.3 (10% slurry) for dihydrate;
pH = 10.4 (10% slurry) for anhydrous material.
Angle of repose: 37.6° for *Compactrol*.(2)
Compressibility: *see* Figure 1.

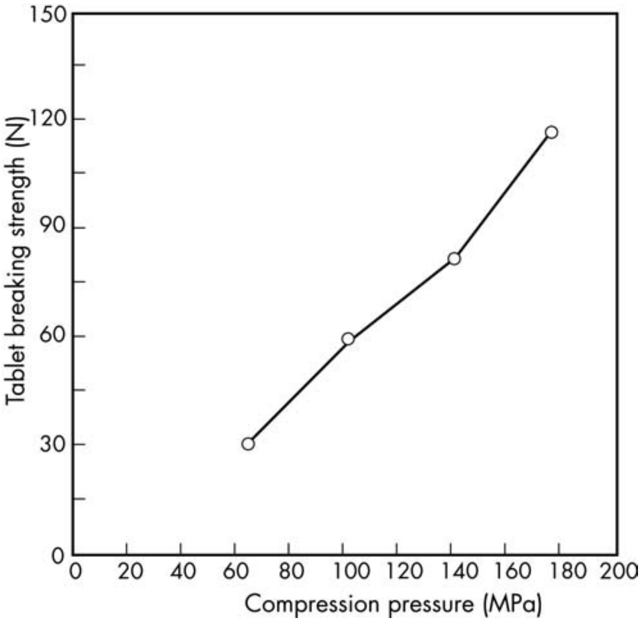

Figure 1: Compression characteristics of calcium sulfate dihydrate. Tablet weight: 700 mg.

Density (bulk):
0.94 g/cm^3 for *Compactrol*;$^{(2)}$
0.67 g/cm^3 for dihydrate;
0.70 g/cm^3 for anhydrous material.
Density (tapped):
1.10 g/cm^3 for *Compactrol*;$^{(2)}$
1.12 g/cm^3 for dihydrate;
1.28 g/cm^3 for anhydrous material.
Density (true): 2.308 g/cm^3
Flowability: 48.4% (Carr compressibility index); 5.2 g/s for *Compactrol*.$^{(2)}$
Melting point: 1450°C for anhydrous material.
Particle size distribution: 93% less than 45 μm in size for the dihydrate (*USG Terra Alba*); 97% less than 45 μm in size for the anhydrous material (*Snow White*). Average particle size is 17 μm for the dihydrate and 8 μm for the anhydrous material. For *Compactrol*, not less than 98% passes through a #40 screen (425 μm), and not less than 85% is retained in a #140 screen (100 μm).
Solubility: *see* Table II.

Table II: Solubility of calcium sulfate dihydrate.

Solvent	Solubility at 20°C unless otherwise stated
Ethanol (95%)	Practically insoluble
Water	1 in 375
	1 in 485 at 100°C

Specific gravity:
2.32 for dihydrate;
2.96 for anhydrous material.
Specific surface area: 3.15 m^2/g (Strohlein apparatus)

11 Stability and Storage Conditions

Calcium sulfate is chemically stable. Anhydrous calcium sulfate is hygroscopic and may cake on storage. Store in a well-closed container in a dry place, avoiding heat.

12 Incompatibilities

In the presence of moisture, calcium salts may be incompatible with amines, amino acids, peptides, and proteins, which may form complexes. Calcium salts will interfere with the bioavailability of tetracycline antibiotics.$^{(5)}$ It is also anticipated that calcium sulfate would be incompatible with indomethacin,$^{(6)}$ aspirin,$^{(7)}$ aspartame,$^{(8)}$ ampicillin,$^{(9)}$ cephalexin,$^{(10)}$ and erythromycin$^{(11)}$ since these materials are incompatible with other calcium salts.

Calcium sulfate may react violently, at high temperatures, with phosphorus and aluminum powder; it can react violently with diazomethane.

13 Method of Manufacture

Anhydrous calcium sulfate occurs naturally as the mineral anhydrite. The naturally occurring rock gypsum may be crushed and ground for use as the dihydrate or calcined at 150°C to produce the hemihydrate. A purer variety of calcium sulfate may also be obtained chemically by reacting calcium carbonate with sulfuric acid or by precipitation from calcium chloride and a soluble sulfate.

14 Safety

Calcium sulfate dihydrate is used as an excipient in oral capsule and tablet formulations. At the levels at which it is used as an excipient, it is generally regarded as nontoxic. However, ingestion of a sufficiently large quantity can result in obstruction of the upper intestinal tract after absorption of moisture.

Owing to the limited intestinal absorption of calcium from its salts, hypercalcemia cannot be induced even after the ingestion of massive oral doses.

Calcium salts are soluble in bronchial fluid. Pure salts do not induce pneumoconiosis.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. The fine-milled grades can generate nuisance dusts that may be irritant to the eyes or on inhalation. The use of a respirator or dust mask is recommended to prevent excessive powder inhalation since excessive inhalation may saturate the bronchial fluid, leading to precipitation and thus blockage of the air passages.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules, sustained release, tablets). Included in nonparenteral medicines licensed in the UK and Europe. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Calcium phosphate, dibasic anhydrous; calcium phosphate, dibasic dihydrate; calcium phosphate, tribasic; calcium sulfate hemihydrate.

Calcium sulfate hemihydrate

Empirical formula: $CaSO_4 \cdot \frac{1}{2}H_2O$
Molecular weight: 145.14
CAS number: [26499-65-0]
Synonyms: annalin; calcii sulfas hemihydricus; calcined gypsum; dried calcium sulfate; dried gypsum; E516; exsiccated calcium sulfate; plaster of Paris; sulfate of lime; yeso blanco.
Appearance: a white or almost white, odorless, crystalline, hygroscopic powder.
Solubility: practically insoluble in ethanol (95%); slightly soluble in water; more soluble in dilute mineral acids.
Comments: the BP 2004 defines dried calcium sulfate as predominantly the hemihydrate, produced by drying powdered gypsum ($CaSO_4 \cdot 2H_2O$) at about 150°C, in a controlled manner, such that minimum quantities of the anhydrous material are produced. Dried calcium sulfate may also contain suitable setting accelerators or decelerators.

18 Comments

Calcium sulfate will absorb moisture and therefore should be used with caution in the formulation of products containing drugs that easily decompose in the presence of moisture. A specification for calcium sulfate is contained in the Food Chemicals Codex (FCC). The EINECS number for calcium sulfate is 231-900-3.

19 Specific References

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22 Date of Revision

26 August 2005.

Canola Oil

1 Nonproprietary Names

None adopted.

2 Synonyms

Canbra oil; *Colzao CT*; *Lipex 108*; *Lipex 204*; *Lipovol CAN*; low erucic acid colza oil; low erucic acid rapeseed oil.

3 Chemical Name and CAS Registry Number

Canola oil [120962-03-0]

4 Empirical Formula and Molecular Weight

Canola oil contains approximately 6% saturated acids, 2% monounsaturated acids, and 32% polyunsaturated acids; *see* Table I. Additionally, sulfur-containing fatty acids may also be present as minor constituents.

Table I: Typical composition of glycerides present in canola oil.

Glyceride	Amount present (%)
Erucic acid	0.2–1.8
Palmitic acid	3.0–4.5
Palmitoleic acid	0.2–0.3
Stearic acid	1.3–1.7
Linoleic acid	19.0–24.0
Oleic acid	56.0–62.0

The sulfur-containing compounds have been held responsible for the unpleasant odors from heated rapeseed oil. It has been suggested that the sulfur compounds in rapeseed oil are of three types: volatile, thermolabile, and nonvolatile.(1)

Unrefined canola oil is said to contain low levels of sulfur-containing fatty acids, resulting in the presence of sulfur in the oil in the stable form of triglycerides. These triglycerides resist refining procedures.(2) *See* Table II for the sulfur content of crude, refined, and deodorized canola oils.(3)

Table II: Total sulfur content in crude, refined and bleached and deodorized canola oil.(a)

Oil sample	Range (mg/kg)	Mean	Standard deviation
Crude	23.6–24.1	23.8	1.0
Refined	19.1–20.2	19.7	2.85
Bleached and deodorized	15.6–16.5	16.2	2.7

(a) Determined using five replicates of each sample analyzed by ion chromatography.

5 Structural Formula

See Section 4.

6 Functional Category

Lubricant; oleaginous vehicle.

7 Applications in Pharmaceutical Formulation or Technology

Canola oil is a refined rapeseed oil obtained from particular species of rapeseed that have been genetically selected for their low erucic acid content.(4) In pharmaceutical formulations, canola oil is used mainly in topical preparations such as soft soaps and liniments. It is also used in cosmetics.

8 Description

A clear, light yellow-colored oily liquid with a bland taste.

9 Pharmacopeial Specifications

—

10 Typical Properties

Acid value: $\leqslant 0.5$
Density: 0.913–0.917 g/cm^3
Erucic acid: $\leqslant 2.0\%$
Flash point: 290–330°C
Free fatty acid: $\leqslant 0.05\%$ as oleic acid
Freezing point: −10 to −2°C
Iodine number: 94–126
Refractive index: n_D^{40} = 1.465–1.469
Saponification value: 186–198
Solubility: soluble in chloroform and ether; practically insoluble in ethanol (95%); miscible with fixed oils.
Viscosity (dynamic): 77.3–78.3 mPa s (77.3–78.3 cP) at 20°C

11 Stability and Storage Conditions

Canola oil is stable and should be stored in an airtight, light-resistant container in a cool, dry place. During storage, grassy, paintlike, or rancid off-flavors can develop.

Flavor deterioration has been attributed mainly to secondary oxidation products of linolenic acid, which normally makes up 9–15% of the fatty acids in canola oil. Storage tests of canola oil showed sensory changes after 2–4 days at 60–65°C in comparison to 16 weeks at room temperature. Canola oil seems to be more stable to storage in light than cottonseed oil and soybean oils, but is less stable than sunflower oil.(5) In addition, the effects of various factors on sediment formation in canola oil have been reported.(6)

It has been reported that oils stored at 2°C showed the highest rate of sediment formation, followed by those stored at 6°C.(5) All samples showed little sediment formation, as measured by turbidity, during storage at 12°C. Removal of sediment from canola oil prior to storage by cold precipitation and filtration did not eliminate this phenomenon, which still developed rapidly at 2°C.

A study on the effect of heating on the oxidation of low linolenic acid canola oil at frying temperatures under nitrogen and air clearly showed that a significantly lower development of oxidation was evident for the low linolenic acid canola oil. Reduction in the linolenic acid content of canola oil reduced the development of room odor at frying temperatures.

12 Incompatibilities

—

13 Method of Manufacture

Canola oil is obtained by mechanical expression or *n*-hexane extraction from the seeds of *Brassica napus (Brassica campestris)* var. *oleifera* and certain other species of *Brassica* (Cruciferae). The crude oil thus obtained is refined, bleached, and deodorized to substantially remove free fatty acids, phospholipids, color, odor and flavor components, and miscellaneous nonoil materials.

14 Safety

Canola oil is generally regarded as an essentially nontoxic and nonirritant material and has been accepted by the FDA for use in cosmetics, foods, and pharmaceuticals.

Rapeseed oil has been used for a number of years in food applications as a cheap alternative to olive oil. However, there are large amounts of erucic acid and glucosinolates in conventional rapeseed oil, both substances being toxic to humans and animals.(7) Canola oil derived from genetically selected rapeseed plants that are low in erucic acid content has been developed to overcome this problem.

Feeding studies in rats have suggested that canola oil is nontoxic to the heart, although it has also been suggested that the toxicological data may be unclear.(8)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Spillages of this material are very slippery and should be covered with an inert absorbent material prior to disposal. Canola oil poses a slight fire hazard.

16 Regulatory Status

Accepted for use by the FDA in cosmetics and foods. Included in the FDA Inactive Ingredients Guide (oral capsules). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Almond oil; corn oil; cottonseed oil; peanut oil; rapeseed oil; sesame oil; soybean oil.

Rapeseed oil

CAS number: [8002-13-9]
Synonyms: *Calchem H-102*; colza oil; rape oil.
Appearance: a clear, yellow to dark yellow-colored oily liquid.
Iodine number: 94–120
Peroxide value: <5
Saponification value: 168–181
Comments: rapeseed oil contains 40–55% erucic acid. It is an edible oil and has been primarily used as an alternative, in foods and some pharmaceutical applications, to the more expensive olive oil. However, the safety of rapeseed oil as part of the diet has been questioned; *see* Section 14.

18 Comments

Canola oil has the lowest level of saturated fat compared to all other oils on the market at present. It has both a high protein (28%) and a high oil content (40%). When the oil is extracted, a high-quality and highly palatable feed concentrate of 37% protein remains. Canola oil is also high in the monounsaturated fatty acid oleic acid; *see* Table III.

The content of tocopherol, a natural antioxidant in canola, is comparable to those of peanut and palm oil. This is an important factor for oils with high linolenic acid content, which can reduce the shelf-life of the product, while the natural antioxidant, if present, can prevent oxidation during storage and processing.

Suggested specifications for refined, bleached, and deodorized canola oil are shown in Table IV. A specification for canola oil is contained in the Food Chemicals Codex (FCC).

The EINECS number for canola oil is 232-313-5.

Table III: Comparison of the composition of crude soybean, canola, palm, and peanut oils.

Components	Canola	Palm	Peanut	Soybean
Fatty acid (%)	0.4–1.0	4.6	0.5–1.0	0.3–0.7
Phosphatides (gum) (%)	3.6	0.05–0.1	0.3–0.4	1.2–1.5
Sterols/triterpene alcohol (%)	0.53	0.1–0.5	0.2	0.33
Tocopherols (%)	0.06	0.003–0.1	0.02–0.06	0.15–0.21
Carotenoids (mg/kg)	25–50	500–1600	>1	40–50
Chlorophyll/ pheophytins (ppm)	5–25	—	—	1–2
Sulfur (ppm)	—	—	—	12–17
Iodine value	112–131	44–60	84–100	123–139

Table IV: Suggested specifications for canola oil.

Test	Minimum	Maximum
Acid value	—	6
Iodine value	110	126
Heavy metal (as lead)	—	5 mg/kg
Refractive index n_D^{40}	1.465	1.467
Free fatty acid (as oleic)	—	0.05%
Erucic acid	—	2%
Moisture and impurities	—	0.05%
Saponification value (mg KOH/g oil)	182	193
Unsaponifiable matter	—	15 g/kg

19 Specific References

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20 General References

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21 Authors

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22 Date of Revision

22 August 2005.

Carbomer

1 Nonproprietary Names

BP: Carbomers
PhEur: Carbomera
USPNF: Carbomer
Note that the USPNF 23 contains several individual carbomer monographs; *see* Sections 4 and 9.

2 Synonyms

Acritamer; acrylic acid polymer; *Carbopol*; carboxy polymethylene, polyacrylic acid; carboxyvinyl polymer; *Pemulen*; *Ultrez*.

3 Chemical Name and CAS Registry Number

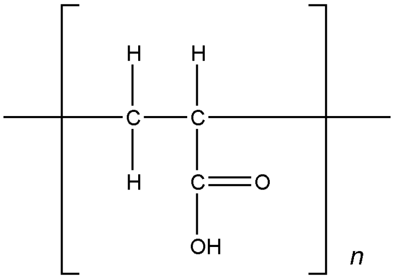
Carbomer [9003-01-4]

Note that carbomer 910, 934, 934P, 940, 941, 971P and 974P resins share the common CAS registry number 9003-01-4. Carbomer 1342 is a copolymer and has a different CAS registry number.

4 Empirical Formula and Molecular Weight

Carbomers are synthetic high-molecular-weight polymers of acrylic acid that are crosslinked with either allyl sucrose or allyl ethers of pentaerythritol. They contain between 56% and 68% of carboxylic acid (COOH) groups calculated on the dry basis. The BP 2004 and PhEur 2005 have a single monograph describing carbomer; the USPNF 23 contains several monographs describing individual carbomer grades that vary in aqueous viscosity and in labeling for oral or non-oral use. The molecular weight of carbomer resins is theoretically estimated at 7×10^5 to 4×10^9. In an effort to measure the molecular weight between crosslinks, M_C, researchers have extended the network theory of elasticity to swollen gels and have utilized the inverse relationship between the elastic modulus and M_C.(1–3) Estimated M_C values of 237 600 g/mol for *Carbopol 941* and of 104 400 g/mol for *Carbopol 940* have been reported.(4) In general, carbomer resins with lower viscosity and lower rigidity will have higher M_C values. Conversely, higher-viscosity, more rigid carbomer resins will have lower M_C values.

5 Structural Formula



Acrylic acid monomer unit in carbomer resins.

Carbomer polymers are formed from repeating units of acrylic acid. The monomer unit is shown above. The polymer chains are crosslinked with allyl sucrose or allyl pentaerythritol. *See also* Section 4.

6 Functional Category

Bioadhesive; emulsifying agent; release-modifying agent; suspending agent; tablet binder; viscosity-increasing agent.

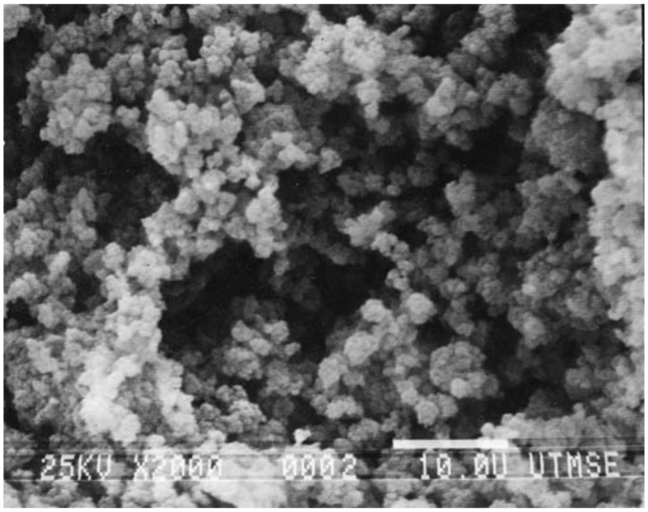
7 Applications in Pharmaceutical Formulation or Technology

Carbomers are mainly used in liquid or semisolid pharmaceutical formulations as suspending or viscosity-increasing agents. Formulations include creams, gels, and ointments for use in ophthalmic,(5–7) rectal,(8–10) and topical preparations.(11–17) Carbomer grades, even with a low residual benzene content, such as carbomer 934P, are no longer included in the PhEur 2005. However, carbomer having low residuals only of other solvents than the ICH-defined 'Class I OVI solvents' may be used in Europe. Carbomer having low residuals only of ethyl acetate, such as carbomer 971P or 974P, may be used in oral preparations, in suspensions, tablets, or sustained release tablet formulations.(18–22) In tablet formulations, carbomers are used as dry or wet binders and as a rate controlling excipient. In wet granulation processes, water or an alcohol–water blend is used as the granulating fluid. Anhydrous organic solvents have also been used, with the inclusion of a polymeric binder. The tackiness of the wet mass can be reduced with the addition of certain cationic species to the granulating fluid(23) or, in the case of water, with talc in the formulation. Carbomer resins have also been investigated in the preparation of sustained-release matrix beads,(23) as enzyme inhibitors of intestinal proteases in peptide-containing dosage forms,(24,25) as a bioadhesive for a cervical patch(26) and for intranasally administered microspheres,(27) in magnetic granules for site-specific drug delivery to the esophagus(28) and in oral mucoadhesive controlled drug delivery systems.(29,30) Carbomers are also employed as emulsifying agents in the preparation of oil-in-water emulsions for external use. For this purpose, the carbomer is neutralized partly with sodium hydroxide and partly with a long-chain amine such as stearylamine. Carbomer 951 has been investigated as a viscosity-increasing aid in the preparation of multiple emulsion microspheres.(31) Carbomers are also used in cosmetics. Therapeutically, carbomer gel formulations have proved efficacious in improving symptoms of moderate-to-severe dry eye syndrome.(32,33) *See* Table I.

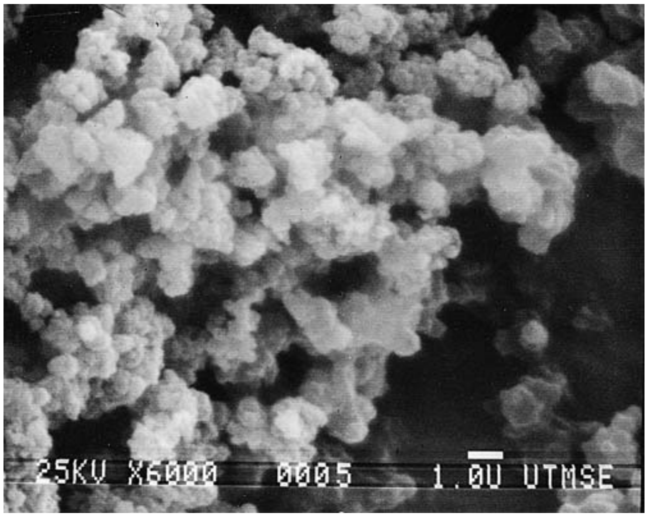
Table I: Uses of carbomers.

Use	Concentration (%)
Emulsifying agent	0.1–0.5
Gelling agent	0.5–2.0
Suspending agent	0.5–1.0
Tablet binder	5.0–10.0

SEM: 1
Excipient: Carbomer 971P (*Carbopol 971P*)
Manufacturer: BF Goodrich
Magnification: 2000×
Voltage: 25 kV



SEM: 2
Excipient: Carbomer 971P (*Carbopol 971P*)
Manufacturer: BF Goodrich
Magnification: 6000×
Voltage: 25 kV



8 Description

Carbomers are white-colored, 'fluffy', acidic, hygroscopic powders with a slight characteristic odor.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for carbomers.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Aqueous viscosity (mPa s)	300–115 000	—
Carbomer 934 (0.5% w/v)	—	30 500–39 400
Carbomer 934P (0.5% w/v)	—	29 400–39 400
Carbomer 940 (0.5 w/v)	—	40 000–60 000(a)
Carbomer 941 (0.5 w/v)	—	4 000–11 000
Carbomer 1342 (1.0% w/v)	—	9 500–26 500
Loss on drying	⩽3.0%	⩽2.0%
Sulfated ash	⩽4.0%	—
Heavy metals	⩽20 ppm	⩽0.002%
Benzene	⩽2 ppm	—
Carbomer 910	—	⩽0.5%
Carbomer 934	—	⩽0.5%
Carbomer 934P	—	⩽0.01%
Carbomer 940	—	⩽0.5%
Carbomer 941	—	⩽0.5%
Carbomer 1342	—	⩽0.2%
Free acrylic acid	⩽0.25%	—
Organic volatile impurities	—	+
Assay (COOH content)	56.0–68.0%	56.0–68.0%

(a) *See* USPNF 23 Suppl. 1.0 for new method.

Note that the USPNF 23 has several monographs for different carbomer grades, while the BP 2004 and the PhEur 2005 have only a single monograph. Other grades of carbomer meet the existing USPNF 23 standards as indicated above. Carbomer 974P is covered by the monograph for carbomer 934P in the USPNF 23. Likewise, carbomer 980 meets the specifications for carbomer 940; carbomers 971P and 981 meet the monograph limits for carbomer 941. Carbomer resins are also covered either individually or together in other pharmacopeias. Unless otherwise indicated, the test limits shown above apply to all grades of carbomer.

10 Typical Properties

Acidity/alkalinity:
pH = 2.7–3.5 for a 0.5% w/v aqueous dispersion;
pH = 2.5–3.0 for a 1% w/v aqueous dispersion.

Density (bulk): 1.76–2.08 g/cm^3

Density (tapped): 1.4 g/cm^3

Glass transition temperature: 100–105°C

Melting point: decomposition occurs within 30 minutes at 260°C. *See* Section 11.

Moisture content: normal water content is up to 2% w/w. However, carbomers are hygroscopic and a typical equilibrium moisture content at 25°C and 50% relative humidity is 8–10% w/w. The moisture content of a carbomer does not affect its thickening efficiency, but an increase in the moisture content makes the carbomer more difficult to handle because it is less readily dispersed.

Particle size distribution: primary particles average about 0.2 μm in diameter. The flocculated powder particles average 2–7 μm in diameter and cannot be broken down into the primary particles. Recently, a granular carbomer having a particle size in the range 180–425 μm has been introduced. Its bulk and tap densities are also higher than those of other carbomers.

Solubility: soluble in water and, after neutralization, in ethanol (95%) and glycerin.

Although they are described as 'soluble', carbomers do not dissolve but merely swell to a remarkable extent, since they are three-dimensionally crosslinked microgels. Furthermore, the pharmacopeial specifications are unclear, in that neutralization with long-chain aliphatic amines or ethoxylated long-chain amines is required for swellability in ethanol, and with water-soluble amines for swellability in glycerin.

Specific gravity: 1.41

Viscosity (dynamic): carbomers disperse in water to form acidic colloidal dispersions of low viscosity that, when neutralized, produce highly viscous gels. Carbomer powders should first be dispersed into vigorously stirred water, taking care to avoid the formation of indispersible lumps, then neutralized by the addition of a base. The *Carbopol ETD* and *Ultrez 10* series of carbomers was introduced to overcome some of the problems of dispersing the powder into aqueous solvents. These carbomer resins wet quickly yet hydrate slowly, while possessing a lower unneutralized dispersion viscosity. Agents that may be used to neutralize carbomer polymers include amino acids, borax, potassium hydroxide, sodium bicarbonate, sodium hydroxide, and polar organic amines such as triethanolamine. Lauryl and stearyl amines may be used as gelling agents in nonpolar systems. One gram of carbomer is neutralized by approximately 0.4 g of sodium hydroxide. During preparation of the gel, the solution should be agitated slowly with a broad, paddlelike stirrer to avoid introducing air bubbles. Neutralized aqueous gels are more viscous at pH 6–11. The viscosity is considerably reduced at pH values less than 3 or greater than 12 or in the presence of strong electrolytes.(23,34) Gels rapidly lose viscosity on exposure to ultraviolet light, but this can be minimized by the addition of a suitable antioxidant. *See also* Section 11.

11 Stability and Storage Conditions

Carbomers are stable, hygroscopic materials that may be heated at temperatures below 104°C for up to 2 hours without affecting their thickening efficiency. However, exposure to excessive temperatures can result in discoloration and reduced stability. Complete decomposition occurs with heating for 30 minutes at 260°C. Dry powder forms of carbomer do not support the growth of molds and fungi. In contrast, microorganisms grow well in unpreserved aqueous dispersions and therefore an antimicrobial preservative such as 0.1% w/v chlorocresol, 0.18% w/v methylparaben–0.02% w/v propylparaben, or 0.1% w/v thimerosal should be added. The addition of certain antimicrobials, such as benzalkonium chloride or sodium benzoate, in high concentrations (0.1% w/v) can cause cloudiness and a reduction in viscosity of carbomer dispersions. Aqueous gels may be sterilized by autoclaving(7) with minimal changes in viscosity or pH, provided care is taken to exclude oxygen from the system, or by gamma irradiation, although this technique may increase the viscosity of the formulation.(35,36) At room temperature, carbomer dispersions maintain their viscosity during storage for prolonged periods. Similarly, dispersion viscosity is maintained, or only slightly reduced, at elevated storage temperatures if an antioxidant is included in the formulation or if the dispersion is stored protected from light. Exposure to light causes oxidation that is reflected in a decrease in dispersion viscosity. Stability to light may be improved by the addition of 0.05–0.1% w/v of a water-soluble UV absorber such as benzophenone-2 or benzophenone-4 in combination with 0.05–0.1% w/v edetic acid. The UV stability of carbomer gels may also be improved by using triethanolamine as the neutralizing base; *see* Section 10.

Carbomer powder should be stored in an airtight, corrosion-resistant container in a cool, dry place. The use of glass, plastic, or resin-lined containers is recommended for the storage of formulations containing carbomer. Packaging in aluminum tubes usually requires the formulation to have a pH less than 6.5, and packaging in other metallic tubes or containers necessitates a pH greater than 7.7 to prolong carbomer stability.

12 Incompatibilities

Carbomers are discolored by resorcinol and are incompatible with phenol, cationic polymers, strong acids, and high levels of electrolytes. Certain antimicrobial adjuvants should also be avoided or used at low levels, *see* Section 11. Trace levels of iron and other transition metals can catalytically degrade carbomer dispersions. Intense heat may be generated if a carbomer is in contact with a strong basic material such as ammonia, potassium or sodium hydroxide, or strongly basic amines.

Certain amino-functional actives form water-insoluble complexes with carbomer; often this can be prevented by adjusting the solubility parameter of the fluid phase using appropriate alcohols and polyols.

Carbomers also form pH-dependent complexes with certain polymeric excipients. Adjustment of solubility parameter can also work in this situation.

13 Method of Manufacture

Carbomers are synthetic, high-molecular-weight, crosslinked polymers of acrylic acid. These poly(acrylic acid) polymers are crosslinked with allyl sucrose or allyl pentaerythritol. The polymerization solvent used most commonly was benzene; however, some of the newer commercially available grades of carbomer are manufactured using either ethyl acetate or a cyclohexane–ethyl acetate cosolvent mixture. The *Carbopol ETD* resins are produced in the cosolvent mixture with a proprietary polymerization aid, and these resins are crosslinked with a polyalkenyl polyether.

14 Safety

Carbomers are used extensively in nonparenteral products, particularly topical liquid and semisolid preparations. They may also be used in oral formulations, although only certain grades can be used; *see* Section 18. Acute oral toxicity studies in animals indicate that carbomer 934P has a low oral toxicity, with doses up to 8 g/kg being administered to dogs without fatalities occurring. Carbomers are generally regarded as essentially nontoxic and nonirritant materials; there is no evidence in humans of hypersensitivity reactions to carbomers used topically. In humans, oral doses of 1–3 g of carbomer have been used as a bulk laxative.

LD_{50} (guinea pig, oral): 2.5 g/kg for carbomer 934(37)
LD_{50} (guinea pig, oral): 2.5 g/kg for carbomer 934P
LD_{50} (guinea pig, oral): 2.5 g/kg for carbomer 940
LD_{50} (mouse, IP): 0.04 g/kg for carbomer 934P
LD_{50} (mouse, IP): 0.04 g/kg for carbomer 940
LD_{50} (mouse, IV): 0.07 g/kg for carbomer 934P
LD_{50} (mouse, IV): 0.07 g/kg for carbomer 940
LD_{50} (mouse, oral): 4.6 g/kg for carbomer 934P
LD_{50} (mouse, oral): 4.6 g/kg for carbomer 934
LD_{50} (mouse, oral): 4.6 g/kg for carbomer 940
LD_{50} (rat, oral): 10.25 g/kg for carbomer 910
LD_{50} (rat, oral): 2.5 g/kg for carbomer 934P
LD_{50} (rat, oral): 4.1 g/kg for carbomer 934
LD_{50} (rat, oral): 2.5 g/kg for carbomer 940
LD_{50} (rat, oral): $>$ 1g/kg for carbomer 941

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Excessive dust generation should be minimized to avoid the risk of explosion (lowest explosive concentration is 100 g/m^3). Carbomer dust is irritating to the eyes, mucous membranes, and respiratory tract. In contact with the eye, carbomer dust is difficult to remove with water owing to the gelatinous film that forms; saline should therefore be used for irrigation purposes. Gloves, eye protection, and a dust respirator are recommended during handling.

16 Regulatory Acceptance

Included in the FDA Inactive Ingredients Guide (oral suspensions, tablets; ophthalmic, rectal, and topical preparations transdermal preparations, vaginal suppositories). Included in nonparenteral medicines licensed in Europe. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Polycarbophil.

18 Comments

A number of different carbomer grades are commercially available that vary in their molecular weight, degree of crosslinking, polymer structure, and residual components. These differences account for the specific rheological, handling, and use characteristics of each grade. Carbomer grades that have the polymer backbone modified with long-chain alkyl acrylates are used as polymeric emulsifiers or in formulations requiring increased resistance to ions.

Polycarbophil, poly(acrylic acid) polymers crosslinked with divinyl glycol, is available for bioadhesive or medicinal applications. Carbomers designated with the letter 'P', e.g. carbomer 971P, are the only pharmaceutical grades of polymer accepted for oral or mucosal contact products. These resins are particularly useful in the production of clear gels.

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22 Date of Revision

25 August 2005.

Carbon Dioxide

1 Nonproprietary Names

BP: Carbon dioxide
JP: Carbon dioxide
PhEur: Carbonei dioxidum
USP: Carbon dioxide

2 Synonyms

Carbonic acid gas; carbonic anhydride; E290.

3 Chemical Name and CAS Registry Number

Carbon dioxide [124-38-9]

4 Empirical Formula and Molecular Weight

CO_2 44.01

5 Structural Formula

CO_2

6 Functional Category

Aerosol propellant; air displacement.

7 Applications in Pharmaceutical Formulation or Technology

Carbon dioxide and other compressed gases such as nitrogen and nitrous oxide are used as propellants for topical pharmaceutical aerosols. They are also used in other aerosol products that work satisfactorily with the coarse aerosol spray that is produced with compressed gases, e.g., cosmetics, furniture polish, and window cleaners.(1–3)

The advantages of compressed gases as aerosol propellants are that they are inexpensive; are of low toxicity; and are practically odorless and tasteless. Also, in comparison to liquefied gases, their pressures change relatively little with temperature. However, the disadvantages of compressed gases are that there is no reservoir of propellant in the aerosol and pressure consequently decreases as the product is used. This results in a change in spray characteristics. Additionally, if a product that contains a compressed gas as a propellant is actuated in an inverted position, the vapor phase, rather than the liquid phase, is discharged. Most of the propellant is contained in the vapor phase and therefore some of the propellant will be lost and the spray characteristics will be altered. Also, sprays produced using compressed gases are very wet. Valves, such as the vapor tap or double dip tube, are currently available and will overcome these problems.

Carbon dioxide is also used to displace air from pharmaceutical products by sparging and hence to inhibit oxidation. As a food additive it is used to carbonate beverages and to preserve foods such as bread from spoilage by mold formation, the gas being injected into the space between the product and its packaging.(4,5)

Solid carbon dioxide is also widely used to refrigerate products temporarily, while liquid carbon dioxide, which can be handled at temperatures up to 31°C under high pressure, is used as a solvent for flavors and fragrances primarily in the perfumery and food manufacturing industries.

8 Description

Carbon dioxide occurs naturally as approximately 0.03% v/v of the atmosphere. It is a colorless, odorless, noncombustible gas with a faint acid taste. Solid carbon dioxide, also known as dry ice, is usually encountered as white-colored pellets or blocks.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for carbon dioxide.

Test	JP 2001	PhEur 2005	USP 28
Characters	+	+	—
Production	—	+	—
Total sulfur	—	⩽1 ppm	—
Water	—	⩽67 ppm	⩽150 mg/m^2
Identification	+	+	+
Carbon monoxide	+	⩽5 ppm	⩽0.001%
Sulfur dioxide	—	⩽2 ppm	⩽5 ppm
Nitrogen monoxide and nitrogen dioxide	—	⩽2 ppm	⩽2.5 ppm
Impurities	—	+	—
Limit of ammonia	—	—	⩽0.0025%
Limit of nitric oxide	—	—	⩽2.5 ppm
Acid	+	—	—
Hydrogen phosphide, hydrogen sulfide or reducing organic substances	+	⩽1 ppm	⩽1 ppm
Oxygen and nitrogen	+	—	—
Assay	⩽99.50%	⩽99.50%	⩽99.00%

10 Typical Properties

Boiling point: −56.6°C
Critical pressure: 7.39 MPa (72.9 atm)
Critical temperature: 31.3°C
Density:
0.714 g/cm^3 for liquid at 25°C;
0.742 g/cm^3 for vapor at 25°C.
Flammability: nonflammable
Melting point: sublimes at −78.5°C
Solubility: 1 in about 1 of water by volume at normal temperature and pressure.
Vapor density (absolute): 1.964 g/m^3
Vapor density (relative): 1.53 (air = 1)
Vapor pressure: 6.436 MPa at 25°C
Viscosity (kinematic): 0.14 mm^2/s (0.14 cSt) at −17.8°C

11 Stability and Storage Conditions

Extremely stable and chemically nonreactive. Store in a tightly sealed cylinder. Avoid exposure to excessive heat.

12 Incompatibilities

Carbon dioxide is generally compatible with most materials although it may react violently with various metal oxides or reducing metals such as aluminum, magnesium, titanium, and zirconium. Mixtures with sodium and potassium will explode if shocked.

13 Method of Manufacture

Carbon dioxide is obtained industrially in large quantities as a by-product in the manufacture of lime; by the incineration of coke or other carbonaceous material; and by the fermentation of glucose by yeast. In the laboratory it may be prepared by dropping acid on a carbonate.

14 Safety

In formulations, carbon dioxide is generally regarded as an essentially nontoxic material.

See also Section 15.

15 Handling Precautions

Handle in accordance with standard procedures for handling metal cylinders containing liquefied or compressed gases. Carbon dioxide is an asphyxiant and inhalation in large quantities is hazardous. It should therefore be handled in a well-ventilated environment equipped with suitable safety devices for monitoring vapor concentration.

It should be noted that carbon dioxide is classified as a greenhouse gas responsible for global warming. At the present time there are no restrictions on its use for aerosols and other applications.

In the UK, the occupational exposure limits for carbon dioxide are 9150 mg/m^3 (5000 ppm) long-term (8-hour TWA) and 27 400 mg/m^3 (15 000 ppm) short-term (15-minute).(6) In the USA, the permissible exposure limits are 9000 mg/m^3 (5000 ppm) long-term and the recommended exposure limits are 18 000 mg/m^3 (10 000 ppm) short-term and 54 000 mg/m^3 (30 000 ppm) maximum, short-term.(7)

Solid carbon dioxide can produce severe burns in contact with the skin and appropriate precautions, depending on the circumstances and quantity of material handled, should be taken. A face shield and protective clothing, including thick gloves, are recommended.

16 Regulatory Status

GRAS listed. Accepted for use in Europe as a food additive. Included in the FDA Inactive Ingredients Guide (aerosol formulation for nasal preparations; IM and IV injections). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Nitrogen; nitrous oxide.

18 Comments

Supercritical carbon dioxide has been used in the formation of fine powders of stable protein formulations.(8,9)

Carbon dioxide has also been investigated for its suitability in Aerosol Solvent Extraction Systems (ASES), to generate microparticles of proteins suitable for aerosol delivery from aqueous based solutions.(10)

A specification for carbon dioxide is contained in the Food Chemicals Codex (FCC).

The EINECS number for carbon dioxide is 204-696-9.

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22 Date of Revision

23 August 2005.

Carboxymethylcellulose Calcium

1 Nonproprietary Names

BP: Carmellose calcium
JP: Carmellose calcium
PhEur: Carmellosum calcicum
USPNF: Carboxymethylcellulose calcium

2 Synonyms

Calcium carboxymethylcellulose; calcium CMC; *ECG 505*; *Nymcel ZSC*.

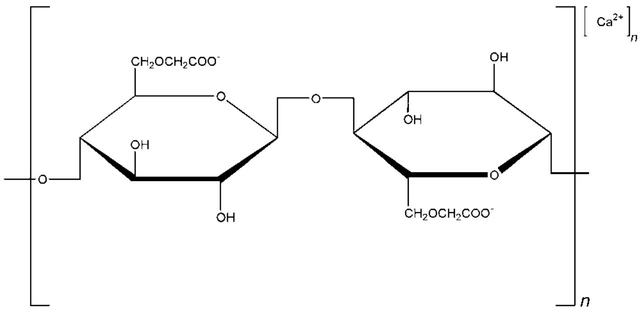
3 Chemical Name and CAS Registry Number

Cellulose, carboxymethyl ether, calcium salt [9050-04-8]

4 Empirical Formula and Molecular Weight

The USPNF 23 describes carboxymethylcellulose calcium as the calcium salt of a polycarboxymethyl ether of cellulose.

5 Structural Formula



Structure shown with a degree of substitution (DS) of 1.0.

6 Functional Category

Stabilizing agent; suspending agent; tablet and capsule disintegrant; viscosity-increasing agent; water-absorbing agent.

7 Applications in Pharmaceutical Formulation or Technology

The main use of carboxymethylcellulose calcium is in tablet formulations (*see* Table I), where it is used as a binder, diluent, and disintegrant.(1–4) Although carboxymethylcellulose calcium is insoluble in water, it is an effective tablet disintegrant as it swells to several times its original bulk on contact with water. Concentrations up to 15% w/w may be used in tablet formulations; above this concentration, tablet hardness is reduced.

Carboxymethylcellulose calcium is also used in other applications similarly to carboxymethylcellulose sodium; for example, as a suspending or viscosity-increasing agent in oral and topical pharmaceutical formulations. Carboxymethylcellulose calcium is also used in modern wound dressings for its water absorption, retention and hemostatic properties.

Table I: Uses of carboxymethylcellulose calcium.

Use	Concentration (%)
Tablet binder	5–15
Tablet disintegrant	1–15

8 Description

Carboxymethylcellulose calcium occurs as a white to yellowish-white, hygroscopic, fine powder.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for carboxymethylcellulose calcium.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Alkalinity	+	+	+
pH	4.5–6.0	—	—
Loss on drying	$\leqslant 10.0\%$	$\leqslant 10.0\%$	$\leqslant 10.0\%$
Residue on ignition	10.0–20.0%	10.0–20.0%	10.0–20.0%
Chloride	$\leqslant 0.360\%$	$\leqslant 0.36\%$	$\leqslant 0.36\%$
Silicate	$\leqslant 0.5\%$	$\leqslant 0.60\%$	$\leqslant 1.5\%$
Sulfate	$\leqslant 0.960\%$	$\leqslant 1.0\%$	$\leqslant 0.96\%$
Arsenic	$\leqslant 10$ ppm	—	—
Heavy metals	$\leqslant 20$ ppm	$\leqslant 20$ ppm	$\leqslant 0.002\%$
Starch	+	—	+
Organic volatile impurities	—	—	+

10 Typical Properties

Acidity/alkalinity: pH = 4.5–6.0 for a 1% w/v aqueous dispersion.

Particle size distribution: 95% through a 73.7 μm sieve (#200 mesh).

Solubility: practically insoluble in acetone, chloroform, ethanol (95%), and ether. Insoluble in water, but swells to twice its volume to form a suspension. Insoluble in 0.1 mol/L hydrochloric acid, but slightly soluble in 0.1 mol/L sodium hydroxide.

11 Stability and Storage Conditions

Carboxymethylcellulose calcium is a stable, though hygroscopic material. It should be stored in a well-closed container in a cool, dry place.

See also Carboxymethylcellulose sodium.

12 Incompatibilities

See Carboxymethylcellulose sodium.

13 Method of Manufacture

Cellulose, obtained from wood pulp or cotton fibers, is carboxymethylated, followed by conversion to the calcium salt. It is then graded on the basis of its degree of carboxymethylation and pulverized.

14 Safety

Carboxymethylcellulose calcium is used in oral and topical pharmaceutical formulations, similarly to carboxymethylcellulose sodium, and is generally regarded as a nontoxic and nonirritant material. However, as with other cellulose derivatives, oral consumption of large amounts of carboxymethylcellulose calcium may have a laxative effect.

See also Carboxymethylcellulose sodium.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Carboxymethylcellulose calcium may be irritant to the eyes; eye protection is recommended.

16 Regulatory Status

Accepted for use as a food additive in Japan at concentrations up to 2% w/w. Included in the FDA Inactive Ingredients Guide (oral, capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Carboxymethylcellulose sodium; croscarmellose sodium.

18 Comments

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19 Specific References

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20 General References

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21 Authors

D Parsons.

22 Date of Revision

17 August 2005.

Carboxymethylcellulose Sodium

1 Nonproprietary Names

BP: Carmellose sodium
JP: Carmellose sodium
PhEur: Carmellosum natricum
USP: Carboxymethylcellulose sodium

2 Synonyms

Akucell; *Aquasorb*; *Blanose*; cellulose gum; CMC sodium; E466; *Finnfix*; *Nymcel*; SCMC; sodium carboxymethylcellulose; sodium cellulose glycolate; sodium CMC; *Tylose CB*.

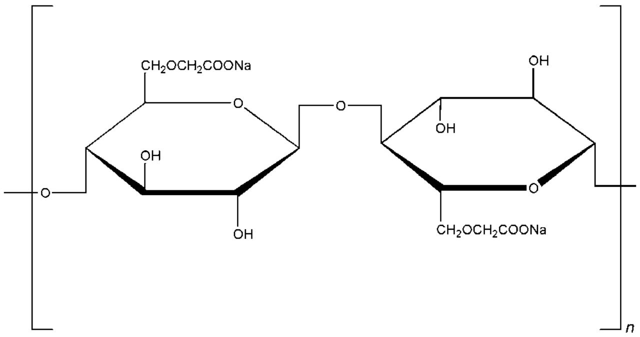
3 Chemical Name and CAS Registry Number

Cellulose, carboxymethyl ether, sodium salt [9004-32-4]

4 Empirical Formula and Molecular Weight

The USP 28 describes carboxymethylcellulose sodium as the sodium salt of a polycarboxymethyl ether of cellulose. Typical molecular weight is 90 000–700 000.

5 Structural Formula



Structure shown with a degree of substitution (DS) of 1.0.

6 Functional Category

Coating agent; stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent; water-absorbing agent.

7 Applications in Pharmaceutical Formulation or Technology

Carboxymethylcellulose sodium is widely used in oral and topical pharmaceutical formulations, primarily for its viscosity-increasing properties. Viscous aqueous solutions are used to suspend powders intended for either topical application or oral and parenteral administration.(1,2) Carboxymethylcellulose sodium may also be used as a tablet binder and disintegrant,(3–6) and to stabilize emulsions.(7,8)

Higher concentrations, usually 3–6%, of the medium-viscosity grade are used to produce gels that can be used as the base for applications and pastes; glycols are often included in such gels to prevent them drying out. Carboxymethylcellulose sodium is additionally one of the main ingredients of self-adhesive ostomy, wound care,(9) and dermatological patches, where it is used as a muco-adhesive and to absorb wound exudate or transepidermal water and sweat. This muco-adhesive property is used in products designed to prevent post-surgical tissue adhesions;(10–12) and to localize and modify the release kinetics of active ingredients applied to mucous membranes; and for bone repair. Encapsulation with carboxymethylcellulose sodium can affect drug protection and delivery.(6,13) There have also been reports of its use as a cytoprotective agent.(14,15)

Carboxymethylcellulose sodium is also used in cosmetics, toiletries,(16) surgical prosthetics,(17) and incontinence, personal hygiene, and food products.

See Table I.

Table I: Uses of carboxymethylcellulose sodium.

Use	Concentration (%)
Emulsifying agent	0.25–1.0
Gel-forming agent	3.0–6.0
Injections	0.05–0.75
Oral solutions	0.1–1.0
Tablet binder	1.0–6.0

8 Description

Carboxymethylcellulose sodium occurs as a white to almost white, odorless, granular powder. *See also* Section 18.

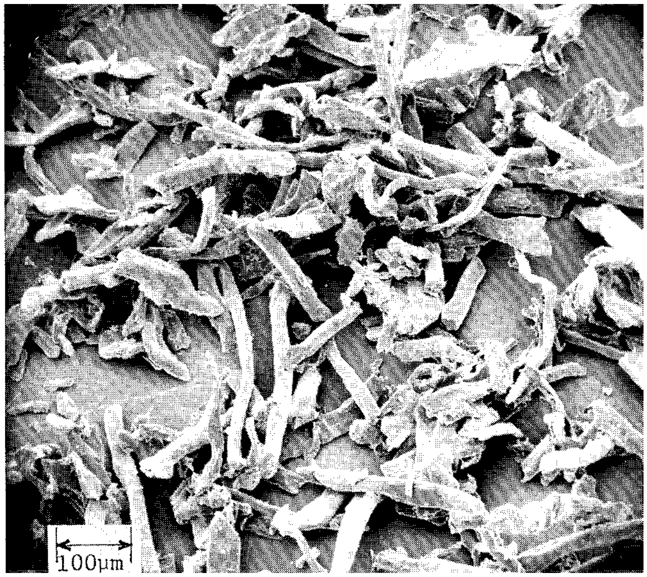
9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for carboxymethylcellulose sodium.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	+	+	—
pH (1% w/v solution)	6.0–8.0	6.0–8.0	6.5–8.5
Appearance of solution	+	+	—
Viscosity	+	+	+
Loss on drying	⩽10.0%	⩽10.0%	⩽10.0%
Heavy metals	⩽20 ppm	⩽20 ppm	⩽20 µg/g
Chloride	⩽0.640%	⩽0.25%	—
Arsenic	⩽10 ppm	—	—
Sulfate	⩽0.960%	—	—
Silicate	⩽0.5%	—	—
Sodium glycolate	—	⩽0.4%	—
Starch	+	—	—
Sulfated ash	—	20.0–33.3%	—
Organic volatile impurities	—	—	+
Assay (of sodium)	6.5–8.5%	6.5–10.8%	6.5–9.5%

SEM: 1
Excipient: Carboxymethylcellulose sodium
Manufacturer: Buckeye Cellulose Corp.
Lot No.: 9247 AP
Magnification: 120×
Voltage: 10 kV



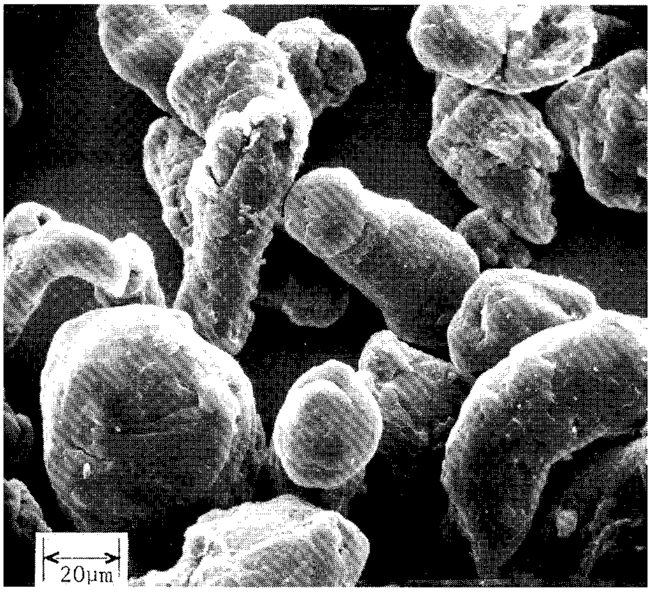
10 Typical Properties

Density (bulk): 0.52 g/cm^3
Density (tapped): 0.78 g/cm^3
Dissociation constant: pK_a = 4.30
Melting point: browns at approximately 227°C, and chars at approximately 252°C.
Moisture content: typically contains less than 10% water. However, carboxymethylcellulose sodium is hygroscopic and absorbs significant amounts of water at temperatures up to 37°C at relative humidities of about 80%. *See* Section 11. *See also* Figure 1.
Solubility: practically insoluble in acetone, ethanol (95%), ether, and toluene. Easily dispersed in water at all temperatures, forming clear, colloidal solutions. The aqueous solubility varies with the degree of substitution (DS). *See* Section 18.
Viscosity: various grades of carboxymethylcellulose sodium are commercially available that have differing aqueous viscosities; *see* Table III. Aqueous 1% w/v solutions with viscosities of 5–13 000 mPa s (5–13 000 cP) may be obtained. An increase in concentration results in an increase in aqueous solution viscosity.(16) Prolonged heating at high temperatures will depolymerize the gum and permanently decrease the viscosity. The viscosity of sodium carboxymethylcellulose solutions is fairly stable over a pH range of 4–10. The optimum pH range is neutral. *See* Section 11.

Table III: Viscosity of aqueous carboxymethylcellulose sodium 1% w/v solutions. (Measurements made with a Brookfield LVT viscometer at 25°C.)

	Grade	Viscosity (mPa s)	Spindle	Speed
Low viscosity	*Akucell AF 0305*	10–15	#1	60 rpm
Medium viscosity	*Akucell AF 2785*	1500–2500	#3	30 rpm
High viscosity	*Akucell AF 3085*	8000–12000	#4	30 rpm

SEM: 2
Excipient: Carboxymethylcellulose sodium
Manufacturer: Hercules Ltd.
Lot No.: 21 A-1 (44390)
Magnification: 600×
Voltage: 10 kV



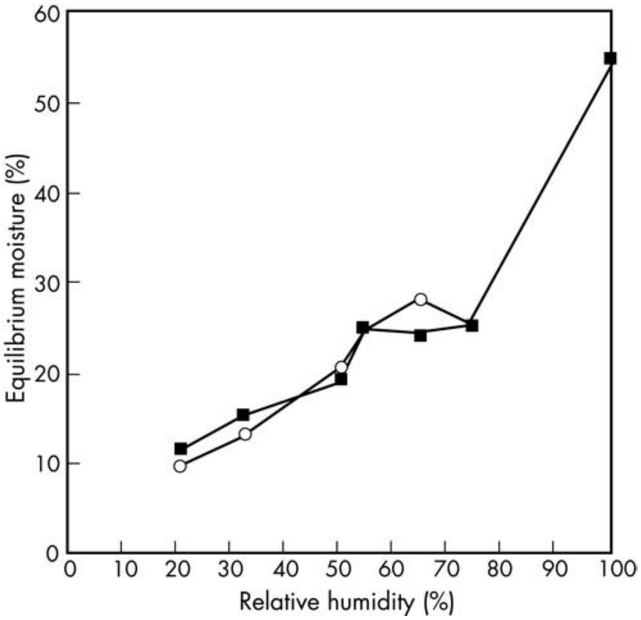


Figure 1: Sorption–desorption isotherm of carboxymethylcellulose sodium.
○: Sorption
■: Desorption

11 Stability and Storage Conditions

Carboxymethylcellulose sodium is a stable, though hygroscopic material. Under high-humidity conditions, carboxymethylcellulose sodium can absorb a large quantity (>50%) of water.

In tablets, this has been associated with a decrease in tablet hardness and an increase in disintegration time.(18)

Aqueous solutions are stable at pH 2–10; precipitation can occur below pH 2, and solution viscosity decreases rapidly above pH 10. Generally, solutions exhibit maximum viscosity and stability at pH 7–9.

Carboxymethylcellulose sodium may be sterilized in the dry state by maintaining it at a temperature of 160°C for 1 hour. However, this process results in a significant decrease in viscosity and some deterioration in the properties of solutions prepared from the sterilized material.

Aqueous solutions may similarly be sterilized by heating, although this also results in some reduction in viscosity. After autoclaving, viscosity is reduced by about 25%, but this reduction is less marked than for solutions prepared from material sterilized in the dry state. The extent of the reduction is dependent on the molecular weight and degree of substitution; higher molecular weight grades generally undergo a greater percentage reduction in viscosity.(19) Sterilization of solutions by gamma irradiation also results in a reduction in viscosity.

Aqueous solutions stored for prolonged periods should contain an antimicrobial preservative.(20)

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Carboxymethylcellulose sodium is incompatible with strongly acidic solutions and with the soluble salts of iron and some other metals, such as aluminum, mercury, and zinc. Precipitation may occur at pH <2, and also when it is mixed with ethanol (95%).

Carboxymethylcellulose sodium forms complex coacervates with gelatin and pectin. It also forms a complex with collagen and is capable of precipitating certain positively charged proteins.

13 Method of Manufacture

Alkali cellulose is prepared by steeping cellulose obtained from wood pulp or cotton fibers in sodium hydroxide solution. The alkaline cellulose is then reacted with sodium monochloroacetate to produce carboxymethylcellulose sodium. Sodium chloride and sodium glycolate are obtained as by-products of this etherification.

14 Safety

Carboxymethylcellulose sodium is used in oral, topical, and some parenteral formulations. It is also widely used in cosmetics, toiletries, and food products, and is generally regarded as a nontoxic and nonirritant material. However, oral consumption of large amounts of carboxymethylcellulose sodium can have a laxative effect; therapeutically, 4–10 g in daily divided doses of the medium- and high-viscosity grades of carboxymethylcellulose sodium have been used as bulk laxatives.(21)

The WHO has not specified an acceptable daily intake for carboxymethylcellulose sodium as a food additive since the levels necessary to achieve a desired effect were not considered to be a hazard to health.(22–25) However, in animal studies, subcutaneous administration of carboxymethylcellulose sodium has been found to cause inflammation, and in some cases of repeated injection fibrosarcomas have been found at the site of injection.(26)

Hypersensitivity and anaphylactic reactions have occurred in cattle and horses, which have been attributed to carboxymethylcellulose sodium in parenteral formulations such as vaccines and penicillins.(27–30)

LD_{50} (guinea pig, oral): 16 g/kg(31)
LD_{50} (rat, oral): 27 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Carboxymethylcellulose sodium may be irritant to the eyes. Eye protection is recommended.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (dental preparations; inhalations; intra-articular, intrabursal, intradermal, intralesional, IM, intrasynovial and SC injections; oral capsules, drops, solutions, suspensions, syrups and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Carboxymethylcellulose calcium.

18 Comments

A number of grades of carboxymethylcellulose sodium are commercially available, such as *Accelerate*. These have a degree of substitution (DS) in the range 0.7–1.2. The DS is defined as the average number of hydroxyl groups substituted per anhydroglucose unit and it is this that determines the aqueous solubility of the polymer. Thermal crosslinking reduces solubility while retaining water absorption, therefore producing materials suitable for water absorption.

Grades are typically classified as being of low, medium, or high viscosity. The degree of substitution and the maximum viscosity of an aqueous solution of stated concentration should be indicated on any carboxymethylcellulose sodium labeling.

Carboxymethylcellulose sodium has been reported to give false positive results in the LAL test for endotoxins.(32)

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20 General References

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21 Authors

D Parsons.

22 Date of Revision

17 August 2005.

Carrageenan

1 Nonproprietary Names

USPNF: Carrageenan

2 Synonyms

Chondrus extract; E407; *Gelcarin*; *Genu*; *Hygum TP-1*; Irish moss extract; *Marine Colloids*; *SeaSpen PF*; *Viscarin*.

3 Chemical Name and CAS Registry Number

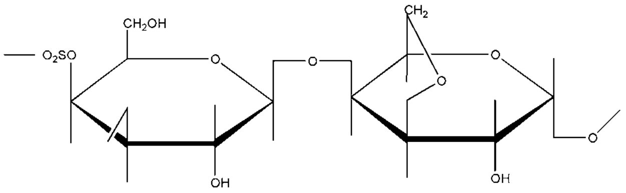
Carrageenan [9000-07-1]
κ-Carrageenan [11114-20-8]
λ-Carrageenan [9064-57-7]

4 Empirical Formula and Molecular Weight

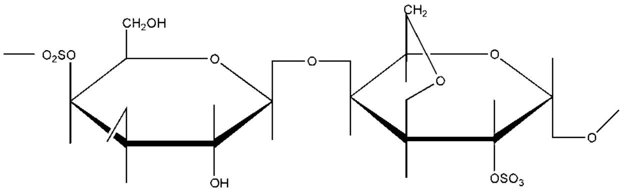
The USPNF 23 describes carrageenan as the hydrocolloid obtained by extraction with water or aqueous alkali from some members of the class Rhodophyceae (red seaweed). It consists chiefly of potassium, sodium, calcium, magnesium, and ammonium sulfate esters of galactose and 3,6-anhydrogalactose copolymers. These hexoses are alternately linked at the α-1,3 and β-1,4 sites in the polymer.

5 Structural Formula

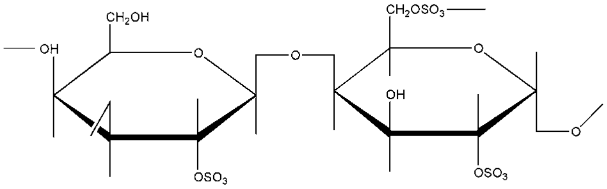
Kappa



Iota



Lambda



The carrageenans are divided into three families according to the position of sulfate groups and the presence or absence of anhydrogalactose.

λ-Carrageenan (lambda-carrageenan) is a nongelling polymer containing about 35% ester sulfate by weight and no 3,6-anhydrogalactose.

ι-Carrageenan (iota-carrageenan) is a gelling polymer containing about 32% ester sulfate by weight and approximately 30% 3,6-anhydrogalactose.

κ-Carrageenan (kappa-carrageenan) is a strongly gelling polymer which has a helical tertiary structure that allows gelling.(1) It contains 25% ester sulfate by weight and approximately 34% 3,6-anhydrogalactose.

6 Functional Category

Emulsifying agent; gel base; stabilizing agent; suspending agent; sustained release tablet matrix; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Carrageenan is used in a variety of nonparenteral dosage forms, including suspensions (wet and reconstitutable), emulsions, gels, creams, lotions, eye drops, suppositories, and tablets and capsules. In suspension formulations, usually only the ι-carrageenen and λ-carrageenan fractions are used. λ-Carrageenan is generally used at levels of 0.7% w/v or less, and provides viscosity to the liquid. Carrageenan has been shown to mask the chalkiness of antacid suspensions when used as a suspending agent in these preparations.(2) When used in concentrations of 0.1–0.5%, carrageenan gives stable emulsions. Carrageenan is used in hand lotions and creams to provide slip and improved ’rub out’.

ι-Carrageenan develops a shear-thinning thixotropic gel, which can be easily poured after shaking. When ι-carrageenan is used, the presence of calcium ions is required for the gel network to become established. With pure ι-carrageenan, about 0.4% w/v is required for most suspensions plus the addition of calcium. However, if *SeaSpen PF* is used, it must be at about 0.75% w/v level, although no additional calcium is required as this is already present in the product to control the rate of gelation.

Studies on the effect of carrageenan and other colloids on muco-adhesion of drugs to the oropharyngeal areas(3,4) have shown that carrageenan had the greatest propensity for adhesion and can be used in formulations for oral and buccal drug delivery.

The application of carrageenan in both topical gel bases and suppository bases has been examined,(5,6) and the findings indicate that the use of carrageenan in these dosage forms is most likely to be dependent on the active drug, owing to the potential for ionic interactions.

In the case of topical gels, a combination of ι, κ-, and λ-carrageenans produces a spreadable gel with acceptable tactile sensation, resulting in drug release that is more likely to follow diffusion kinetics.

In the case of suppository dosage forms, a greater amount of κ-carrageenan is required in the presence of potassium to form a more rigid structure.

Incorporation of carrageenan into tablet matrices with various drugs and other excipients to alter release profiles has been studied, illustrating that the carrageenans have good tablet-binding properties.(7–10) Furthermore, the inclusion of calcium or potassium salts into the tablet creates a microenvironment for gelation to occur, which further controls drug release.

There have also been several references to the use of carrageenan in chewable tablets having a confectionary texture.(11,12) This approach to creating a novel dosage form requires the use of both ι-carrageenan and κ-carrageenan, to prevent moisture loss and texture changes that occur over time.

See also Section 10. Carrageenan has been used for the microencapsulation of proteins(13) and probiotic bacteria.(14) It has also been used as beads in the preparation of controlled release systems.(15,16) Studies have shown that carrageenan compounds block infections by the herpes simplex virus;(17) human cytomegalovirus; human papilloma virus; Sindbis virus; vesicular stomatitis virus; and HIV.(18) A combined κ- and λ-carrageenan formulation is currently being investigated as the active ingredient in a topical microbicide used to prevent the sexual transmission of HIV.(19–21) In combination with chitosan, agar and polyvinyl pyrrolidone, carrageenan forms a water-insoluble complex which is able to absorb large amounts of body fluids, and is used as an effective wound dressing.(22–24) Carrageenan is used in the preparation of hard and soft capsule shells.(25) It is also used in toothpastes and cosmetic preparations such as conditioners and shampoos.(26,27)

8 Description

Carrageenan, when extracted from the appropriate seaweed source, is a yellow-brown to white colored, coarse to fine powder that is odorless and tasteless.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for carrageenan.

Test	USPNF 23
Identification	+
Acid insoluble matter	⩽2.0%
Arsenic	⩽3 ppm
Heavy metals	⩽0.004%
Lead	⩽0.001%
Loss on drying	⩽12.5%
Total ash	⩽35.0%
Viscosity (at 75°C)	⩽5 mPa s
Microbial limits	⩽200 /g

10 Typical Properties

Because of the vast differences in the material that can be referred to as carrageenan, it is difficult to give descriptions of typical properties. *See* Table II.

Solubility: soluble in water at 80°C. *See* Tables II and III.

Viscosity (dynamic): 5 mPa s (5 cP) at 75°C. *See* Table II.

11 Stability and Storage Conditions

Carrageenan is a stable, though hygroscopic, polysaccharide and should be stored in a cool, dry place.

12 Incompatibilities

Carrageenan can react with cationic materials. If complexation of cationic materials, with associated modification of the active compound's solubility, is undesirable, the use of carrageenan is not recommended.

Table III: Solubililty and gelation properties of ι-, κ-, and λ-carrageenans.

	Kappa	Iota	Lambda
Solubility in water			
20°C	Na salt only	Na salt only	Yes
80°C	Yes	Yes	Yes
Gelation			
Ions necessary	K^+	Ca^{2+}	No gel
Texture	Brittle	Elastic	No gel
Re-gelation after shear	No	Yes	—
Acid stability	>pH 3.8	>pH 3.8	—

Table II: Typical properties of different grades of carrageenan (FMC Biopolymer).

Trade name	Carrageenan type	Gel type	Solubility in water	Viscosity	Use concentration (%)	Use examples
Gelcarin GP-379	Iota	Elastic, medium strength	Hot	High, thixotropic	0.3–1.0	Creams, suspensions
Gelcarin GP-812	Kappa	Brittle, strong	Hot	Low	0.3–1.0	Gels
Gelcarin GP-911	Kappa	Brittle, firm	Hot, partial in cold	Low	0.25–2.0	Encapsulation
SeaSpen PF	Iota	Elastic, weak	Cold, delayed gel formation	Medium, thixotropic	0.5–1.0	Creams, suspensions, lotions
Viscarin GP-109	Lambda	Non-gelling	Partial cold, full in hot	Medium	0.1–1.0	Creams, lotions
Viscarin GP-209	Lambda	Non-gelling	Partial cold, full in hot	High	0.1–1.0	Creams, lotions
Viscarin GP-328	Kappa/lambda	Weak	Hot	Medium–high	0.7–1.2	Creams, emulsions, lotions

13 Method of Manufacture

The main species of seaweed from which carrageenan is manufactured are *Eucheuma*, *Chondrus*, and *Gigartina*. The weed is dried quickly to prevent degradation, and is then baled for shipment to processing facilities. The seaweed is repeatedly washed to remove gross impurities such as sand, salt and marine life. The weed undergoes a hot alkali extraction process, releasing the carrageenan from the cell. Once it is in a hot solution, carrageenan undergoes clarification and concentration in solution and is converted to powder.

Three processes can be used to remove the carrageenan from solution. The first is a 'freeze–thaw' technique. The solution is gelled with various salts, then the gels are frozen. Upon thawing, the water is removed and the resultant mass, primarily carrageenan and salt, is ground to the desired particle size.

The second method, referred to as the 'alcohol precipitation method' takes the concentrated solution of carrageenan and places it in alcohol. This causes the carrageenan to precipitate out of solution. The cosolvents are evaporated and the precipitated carrageenan is dried and ground to the desired particle size.

The third method is the 'KCl precipitation' process, where after hot extraction, the filtrate is evaporated to reduce the filtrate volume. The filtrate is then extruded through spinnerets into a cold 1.0–1.5% solution of potassium chloride. The resulting gel threads are washed with KCl solution and are pressed, dried and milled to carrageenan powder.(2) Commercial carrageenan is usually standardized by blending different batches of carrageenan and adding sugar or salt to obtain the desired gelling or thickening properties.(28)

14 Safety

Carrageenan is widely used in numerous food applications and is increasingly being used in pharmaceutical formulations. Carrageenan is generally regarded as a relatively nontoxic and nonirritating material when used in nonparenteral pharmaceutical formulations.

However, carrageenan is known to induce inflammatory responses in laboratory animals, and for this reason it is frequently used in experiments for the investigation of anti-inflammatory drugs.(29,30) Animal studies suggest that degraded carrageenan (which is not approved for use in food products) may be associated with cancer in the intestinal tract, although comparable evidence does not exist in humans.(31)

The WHO has set an acceptable daily intake of carrageenan of 'not specified' as the total daily intake was not considered to represent a hazard to health.(32) In the UK, the Food Advisory Committee has recommended that carrageenan should not be used as an additive for infant formulas.(33)

LD_{50} (rat, oral): >5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (dental; oral granules, powders and syrups, topical; and transdermal preparations). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

—

18 Comments

The EINECS number for carrageenan is 232-524-2.

19 Specific References

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21 Authors

KK Singh.

22 Date of Revision

26 August 2005.

Castor Oil

1 Nonproprietary Names

BP: Virgin castor oil
JP: Castor oil
PhEur: Ricini oleum virginale
USP: Castor oil

2 Synonyms

EmCon CO; *Lipovol CO*; oleum ricini; ricinoleum; ricinus communis; ricinus oil; tangantangan.

3 Chemical Name and CAS Registry Number

Castor oil [8001-79-4]

4 Empirical Formula and Molecular Weight

Castor oil is a triglyceride of fatty acids. The fatty acid composition is approximately ricinoleic acid (87%); oleic acid (7%); linoleic acid (3%); palmitic acid (2%); stearic acid (1%) and trace amounts of dihydroxystearic acid.

5 Structural Formula

See Section 4.

6 Functional Category

Emollient; oleaginous vehicle; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Castor oil is widely used in cosmetics, food products, and pharmaceutical formulations. In pharmaceutical formulations, castor oil is most commonly used in topical creams and ointments at concentrations of 5–12.5%. However, it is also used in oral tablet and capsule formulations and as a solvent in intramuscular injections.(1,2)

Therapeutically, castor oil has been administered orally for its laxative action, but such use is now obsolete.

8 Description

Castor oil is a clear, almost colorless or pale yellow-colored viscous oil. It has a slight odor and a taste that is initially bland but afterwards slightly acrid.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for castor oil.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	—
Characters	+	+	—
Specific gravity	0.953–0.965	≈0.958	0.957–0.961
Heavy metals	—	—	⩽0.001%
Iodine value	80–90	82–90	83–88
Saponification value	176–187	—	176–182
Hydroxyl value	155–177	⩾150	160–168
Acid value	⩽1.5	⩽2.0	—
Peroxide value	—	⩽10.0	—
Refractive index	—	≈1.479	—
Optical rotation	—	+3.5° to +6.0°	—
Water	—	⩽0.3%	—
Absorbance	+	⩽1.5	—
Composition of fatty acids	—	+	—
Purity	+	—	—
Distinction from most other fixed oils	—	—	+
Free fatty acids	—	—	+
Unsaponifiable matter	—	⩽0.8%	—

10 Typical Properties

Autoignition temperature: 449°C
Boiling point: 313°C
Density: 0.955–0.968 g/cm^3 at 25°C
Flash point: 229°C
Melting point: −12°C
Moisture content: ⩽0.25%
Refractive index:
n_D^{25} = 1.473–1.477;
n_D^{40} = 1.466–1.473.
Solubility: miscible with chloroform, diethyl ether, ethanol, glacial acetic acid, and methanol; freely soluble in ethanol (95%) and petroleum ether; practically insoluble in water; practically insoluble in mineral oil unless mixed with another vegetable oil. *See also* Section 11.
Surface tension:
39.0 mN/m at 20°C;
35.2 mN/m at 80°C.
Viscosity (dynamic):
1000 mPa s (1000 cP) at 20°C;
200 mPa s (200 cP) at 40°C.

11 Stability and Storage Conditions

Castor oil is stable and does not turn rancid unless subjected to excessive heat. On heating at 300°C for several hours, castor oil polymerizes and becomes soluble in mineral oil. When cooled to 0°C, it becomes more viscous.

Castor oil should be stored at a temperature not exceeding 25°C in well-filled airtight containers protected from light.

12 Incompatibilities

Castor oil is incompatible with strong oxidizing agents.

13 Method of Manufacture

Castor oil is the fixed oil obtained by cold-expression of the seeds of *Ricinus communis* Linné (Fam. Euphorbiaceae). No other substances are added to the oil.

14 Safety

Castor oil is used in cosmetics and foods and orally, parenterally, and topically in pharmaceutical formulations. It is generally regarded as a relatively nontoxic and nonirritant material when used as an excipient.(3)

Castor oil has been used therapeutically as a laxative and oral administration of large quantities may cause nausea, vomiting, colic, and severe purgation. It should not be given when intestinal obstruction is present.

Although widely used in topical preparations, including ophthalmic formulations, castor oil has been associated with some reports of allergic contact dermatitis, mainly to cosmetics such as lipsticks.(4–7)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Castor oil may cause mild irritation to the skin and eyes. Castor oil is flammable when exposed to heat. Spillages are slippery and should be covered with an inert absorbant before collection and disposal.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (IM injections; oral capsules and tablets; topical creams, emulsions, ointments, and solutions). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Castor oil, hydrogenated.

18 Comments

A specification for castor oil is contained in the Food Chemicals Codex (FCC).

The EINECS number for castor oil is 232-293-8.

19 Specific References

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20 General References

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21 Authors

LME McIndoe.

22 Date of Revision

7 August 2005.

Castor Oil, Hydrogenated

1 Nonproprietary Names

BP: Hydrogenated castor oil
PhEur: Ricini oleum hydrogenatum
USPNF: Hydrogenated castor oil

2 Synonyms

Castorwax; *Castorwax MP 70*; *Castorwax MP 80*; *Croduret*; *Cutina HR*; *Fancol*; *Simulsol 1293*.

3 Chemical Name and CAS Registry Number

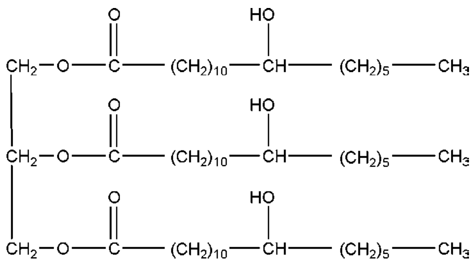
Glyceryl-tri-(12-hydroxystearate) [8001-78-3]

4 Empirical Formula and Molecular Weight

$C_{57}O_9H_{110}$ 939.50

The USPNF 23 describes hydrogenated castor oil as the refined, bleached, hydrogenated, and deodorized castor oil, consisting mainly of the triglyceride of hydroxystearic acid.

5 Structural Formula



6 Functional Category

Extended release agent; stiffening agent; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Hydrogenated castor oil is a hard wax with a high melting point used in oral and topical pharmaceutical formulations; *see* Table I.

In topical formulations, hydrogenated castor oil is used to provide stiffness to creams and emulsions.(1) In oral formulations, hydrogenated castor oil is used to prepare sustained-release tablet and capsule preparations;(2–5) the hydrogenated castor oil may be used as a coat or to form a solid matrix.

Hydrogenated castor oil is additionally used to lubricate the die walls of tablet presses;(6,7) and is similarly used as a lubricant in food processing.

Hydrogenated castor oil is also used in cosmetics.

Table I: Uses of hydrogenated castor oil.

Use	Concentration (%)
Coating agent (delayed release)	5.0–20.0
Delayed release drug matrix	5.0–10.0
Tablet die lubricant	0.1–2.0

8 Description

Hydrogenated castor oil occurs as a fine, almost white or pale yellow powder or flakes. The PhEur 2005 describes hydrogenated castor oil as the oil obtained by hydrogenation of virgin castor oil. It consists mainly of the triglyceride of 12-hydroxystearic acid.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for hydrogenated castor oil.

Test	PhEur 2005	USPNF 23
Characters	+	—
Identification	+	—
Acid value	⩽4.0	—
Hydroxyl value	145–165	154–162
Iodine value	⩽5.0	⩽5.0
Saponification value	—	176–182
Alkaline impurities	+	—
Composition of fatty acids	+	+
Palmitic acid	⩽2.0%	—
Stearic acid	7.0–14%	—
Arachidic acid	⩽1.0%	—
12-Oxostearic acid	⩽5.0%	—
12-Hydroxystearic acid	78.0–91.0%	—
Any other fatty acid	⩽3.0%	—
Nickel	⩽1 ppm	—
Heavy metals	—	⩽0.001%
Melting range	83–88°C	85–88°C

10 Typical Properties

Acid value: ⩽5
Density: 0.98–1.10 g/cm^3
Flash point: 316°C (open cup)
Moisture content: ⩽0.1%
Particle size distribution: 97.7% ⩾1000 μm in size for flakes.
Solubility: practically insoluble in water; soluble in acetone, chloroform, and methylene chloride.

11 Stability and Storage Conditions

Hydrogenated castor oil is stable at temperatures up to 150°C.

Clear, stable, chloroform solutions containing up to 15% w/v of hydrogenated castor oil may be produced. Hydrogenated castor oil may also be dissolved at temperatures greater than 90°C in polar solvents and mixtures of aromatic and polar solvents, although the hydrogenated castor oil precipitates out on cooling below 90°C.

Hydrogenated castor oil should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Hydrogenated castor oil is compatible with most natural vegetable and animal waxes.

13 Method of Manufacture

Hydrogenated castor oil is prepared by the hydrogenation of castor oil using a catalyst.

14 Safety

Hydrogenated castor oil is used in oral and topical pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material.

Acute oral toxicity studies in animals have shown that hydrogenated castor oil is a relatively nontoxic material. Irritation tests with rabbits show that hydrogenated castor oil causes mild, transient irritation to the eye.

LD_{50} (rat, oral): >10 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Accepted in the USA as an indirect food additive. Included in the FDA Inactive Ingredients Guide (oral capsules, tablets, and sublingual tablets).

Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Castor oil; vegetable oil, hydrogenated.

18 Comments

Various different grades of hydrogenated castor oil are commercially available, the composition of which may vary considerably. *Sterotex K* (Karlshamns Lipid Specialities), for example, is a mixture of hydrogenated castor oil and hydrogenated cottonseed oil. *See* Vegetable Oil, hydrogenated for further information. The EINECS number for hydrogenated castor oil is 232-292-2.

19 Specific References

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6 Danish FQ, Parrott EL. Effect of concentration and size of lubricant on flow rate of granules. *J Pharm Sci* 1971; **60**: 752–754.

7 Hölzer AW, Sjögren J. Evaluation of some lubricants by the comparison of friction coefficients and tablet properties. *Acta Pharm Suec* 1981; **18**: 139–148.

20 General References

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21 Authors

RT Guest.

22 Date of Revision

21 August 2005.

Cellulose, Microcrystalline

1 Nonproprietary Names

BP: Microcrystalline cellulose
JP: Microcrystalline cellulose
PhEur: Cellulosum microcristallinum
USPNF: Microcrystalline cellulose

2 Synonyms

Avicel PH; *Celex*; cellulose gel; *Celphere*; *Ceolus KG*; crystalline cellulose; E460; *Emcocel*; *Ethispheres*; *Fibrocel*; *Pharmacel*; *Tabulose*; *Vivapur.*

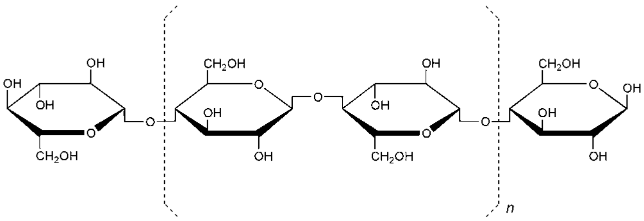
3 Chemical Name and CAS Registry Number

Cellulose [9004-34-6]

4 Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ ≈36 000
where $n \approx 220$.

5 Structural Formula



6 Functional Category

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

7 Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes.(1–7) In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant(8) and disintegrant properties that make it useful in tableting.

Microcrystalline cellulose is also used in cosmetics and food products; *see* Table I.

Table I: Uses of microcrystalline cellulose.

Use	Concentration (%)
Adsorbent	20–90
Antiadherent	5–20
Capsule binder/diluent	20–90
Tablet disintegrant	5–15
Tablet binder/diluent	20–90

8 Description

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

9 Pharmacopeial Specifications

See Table II.

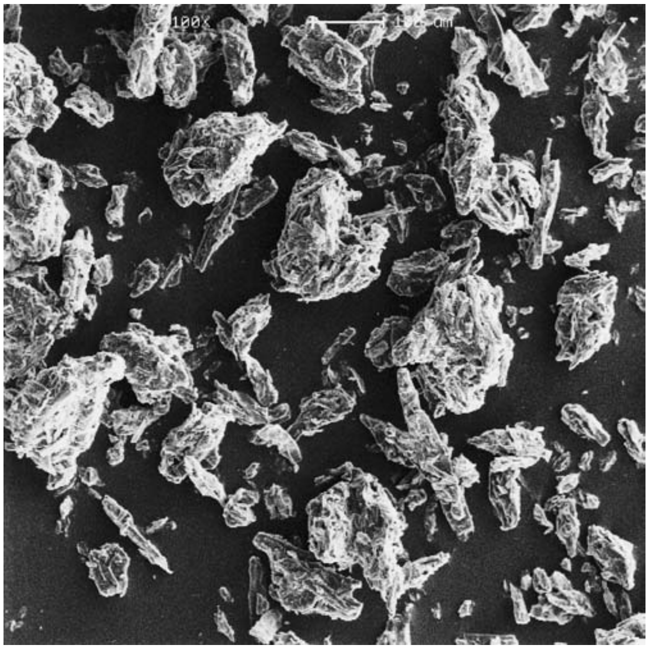
Table II: Pharmacopeial specifications for microcrystalline cellulose.

Test	JP 2001	PhEur 2005 (Suppl 5.1)	USPNF 23
Identification	+	+	+
Characters	+	+	—
pH	5.0–7.0	5.0–7.5	5.0–7.5
Bulk density	+	—	+
Loss on drying	⩽7.0%	⩽7.0%	⩽7.0%
Residue on ignition	⩽0.05%	—	⩽0.1%
Conductivity	+	+	+
Sulfated ash	—	⩽0.1%	—
Ether-soluble substances	⩽0.05%	⩽0.05%	⩽0.05%
Water-soluble substances	+	⩽0.25%	⩽0.25%
Heavy metals	⩽10 ppm	⩽10 ppm	⩽0.001%
Organic volatile impurities	—	—	+
Microbial limits	+	+	+
Aerobic	—	$\leqslant 10^3$/g	⩽1000 cfu/g
Molds and yeasts	—	$\leqslant 10^2$/g	⩽100 cfu/g
Solubility	—	+	—
Particle size distribution	—	—	+

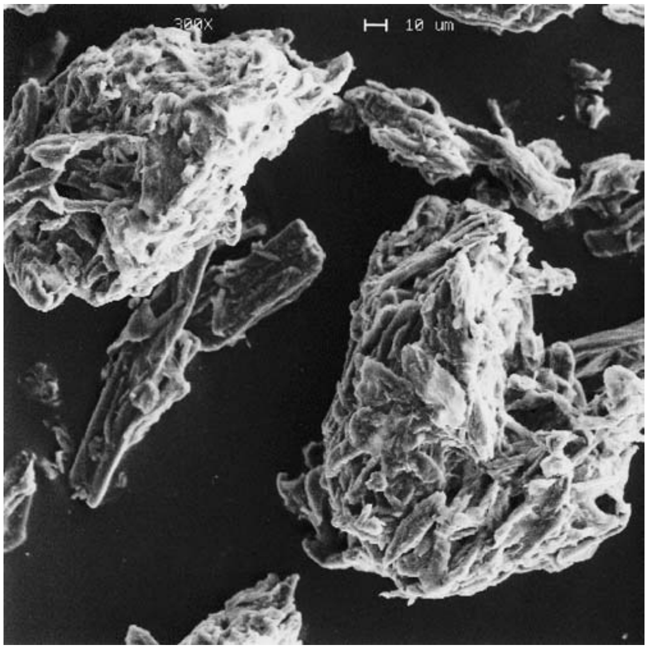
10 Typical Properties

Angle of repose:
49° for *Ceolus KG*;
34.4° for *Emcocel 90M.*(9)
Density (bulk):
0.337 g/cm^3;
0.32 g/cm^3 for *Avicel PH-101*;(10)
0.29 g/cm^3 for *Emcocel 90M*;(9)
0.29 g/cm^3 for *VivaPur 101.*
Density (tapped):
0.478 g/cm^3;
0.45 g/cm^3 for *Avicel PH-101*;
0.35 g/cm^3 for *Emcocel 90M.*(9)
Density (true): 1.512–1.668 g/cm^3
Flowability: 1.41 g/s for *Emcocel 90M.*(9)
Melting point: chars at 260–270°C.
Moisture content: typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.(11) *See* Table III.

SEM: 1
Excipient: Microcrystalline cellulose
Manufacturer: JRS Pharma LP.
Lot No.: 98662
Magnification: 100×

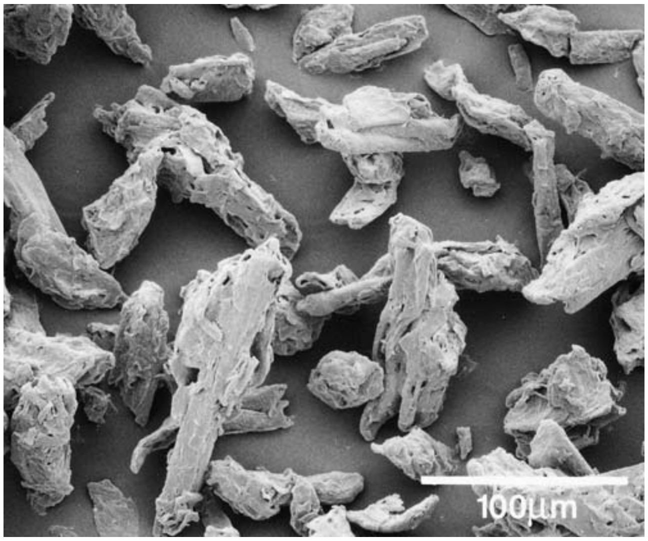


SEM: 2
Excipient: Microcrystalline cellulose
Manufacturer: JRS Pharma LP.
Lot No.: 98662
Magnification: 300×



Particle size distribution: typical mean particle size is 20–200 μm. Different grades may have a different nominal mean particle size; *see* Table III.

SEM: 3
Excipient: Microcrystalline cellulose
Manufacturer: FMC Biopolymer
Magnification: 100×



Solubility: slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Specific surface area:
1.06–1.12 m^2/g for *Avicel PH-101*;
1.21–1.30 m^2/g for *Avicel PH-102*;
0.78–1.18 m^2/g for *Avicel PH-200*.

11 Stability and Storage Conditions

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Microcrystalline cellulose is incompatible with strong oxidizing agents.

13 Method of Manufacture

Microcrystalline cellulose is manufactured by controlled hydrolysis with dilute mineral acid solutions of α-cellulose, obtained as a pulp from fibrous plant materials. Following hydrolysis, the hydrocellulose is purified by filtration and the aqueous slurry is spray-dried to form dry, porous particles of a broad size distribution.

14 Safety

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and nonirritant material.

Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations.

Table III: Properties of selected commercially available grades of microcrystalline cellulose.

Grade	Nominal mean particle size (μm)	Particle size analysis		Moisture content (%)
		Mesh size	Amount retained (%)	
Avicel PH-101[a]	50	60	≤1.0	≤5.0
		200	≤30.0	
Avicel PH-102[a]	100	60	≤8.0	≤5.0
		200	≥45.0	
Avicel PH-103[a]	50	60	≤1.0	≤3.0
		200	≤30.0	
Avicel PH-105[a]	20	400	≤1.0	≤5.0
Avicel PH-112[a]	100	60	≤8.0	≤1.5
Avicel PH-113[a]	50	60	≤1.0	≤1.5
		200	≤30.0	
Avicel PH-200[a]	180	60	≥10.0	≤5.0
		100	≥50.0	
Avicel PH-301[a]	50	60	≤1.0	≤5.0
		200	≤30.0	
Avicel PH-302[a]	100	60	≤8.0	≤5.0
		200	≥45.0	
Celex 101[b]	75	60	≤1.0	≤5.0
		200	≥30.0	
Ceolus KG-802[c]	50	60	≤0.5	≤6.0
		200	≤30.0	
Emcocel 50M[d]	50	60	≤0.25	≤5.0
		200	≤30.0	
Emcocel 90M[d]	91	60	≤8.0	≤5.0
		200	≥45.0	
Vivapur 101[d]	50	60	≤1.0	≤5.0
		200	≤30.0	
Vivapur 102[d]	90	60	≤8.0	≤5.0
		200	≥45.0	
Vivapur 12[d]	160	38	≤1.0	≤5.0
		94	≤50.0	

Suppliers:
[a] FMC Biopolymer
[b] International Specialty Products
[c] Asahi Kasei Corporation
[d] J Rettenmaier & Söhne GmbH

Deliberate abuse of formulations containing cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas.(12)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection, and a dust mask are recommended. In the UK, the occupational exposure limits for cellulose have been set at 10 mg/m^3 long-term (8-hour TWA) for total inhalable dust and 4 mg/m^3 for respirable dust; the short-term limit for total inhalable dust has been set at 20 mg/m^3.(13)

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (inhalations; oral capsules, powders, suspensions, syrups, and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Microcrystalline cellulose and carrageenan; microcrystalline cellulose and carboxymethylcellulose sodium; microcrystalline cellulose and guar gum; powdered cellulose; silicified microcrystalline cellulose.

Microcrystalline cellulose and carrageenan

Synonyms: *Lustre Clear.*

Comments: *Lustre Clear* (FMC Biopolymer) is an aqueous film coating combining microcrystalline cellulose and carrageenan.

Microcrystalline cellulose and carboxymethylcellulose sodium

Synonyms: *Avicel CL-611*; *Avicel RC-581*; *Avicel RC-591*; colloidal cellulose; dispersible cellulose.

Appearance: white, odorless and tasteless, hygroscopic powder.

Acidity/alkalinity: pH = 6–8 for a 1.2% w/v aqueous dispersion.

Moisture content: not more than 6.0% w/w.

Particle size distribution:

Avicel CL-611: ≤0.1% retained on a #60 mesh and ≤50% retained on a #325 mesh;

Avicel RC-581: ≤0.1% retained on a #60 mesh and ≤35% retained on a #200 mesh;

Avicel RC-591: ≤0.1% retained on a #60 mesh and ≤45% retained on a #325 mesh.

Solubility: practically insoluble in dilute acids and organic solvents. Partially soluble in dilute alkali and water (carboxymethylcellulose sodium fraction).

Viscosity (dynamic):

5–20 mPa s (5–20 cP) for a 1.2% w/v aqueous dispersion of *Avicel CL-611*;

72–168 mPa s (72–168 cP) for *Avicel RC-581* at the same concentration;

39–91 mPa s (39–91 cP) for *Avicel RC-591* at the same concentration.

Comments: mixtures of microcrystalline cellulose and carboxymethylcellulose sodium that are dispersible in water and produce thixotropic gels are suitable as suspending vehicles in pharmaceutical formulations. The amount of carboxymethylcellulose present can vary between 8.3% and 18.8% w/w depending upon the grade of material.

Microcrystalline cellulose and guar gum

Synonyms: *Avicel CE-15.*

Comments: *Avicel CE-15* (FMC Biopolymer) is a coprocessed mixture of microcrystalline cellulose and guar gum used in chewable tablet formulations.

18 Comments

Several different grades of microcrystalline cellulose are commercially available that differ in their method of manufacture,(14,15) particle size, moisture, flow, and other physical properties.(16–28) The larger-particle-size grades generally provide better flow properties in pharmaceutical machinery. Low-moisture grades are used with moisture-sensitive materials. Higher-density grades have improved flowability.

Several coprocessed mixtures of microcrystalline cellulose with other excipients such as carrageenan, carboxymethylcellulose sodium, and guar gum are commercially available; *see* Section 17.

Celphere (Asahi Kasei Corporation) is a pure spheronized microcrystalline cellulose available in several different particle size ranges.

A specification for microcrystalline cellulose is contained in the Food Chemicals Codex (FCC).

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21 Authors

LY Galichet.

22 Date of Revision

20 August 2005.

Cellulose, Powdered

1 Nonproprietary Names

BP: Powdered cellulose
JP: Powdered cellulose
PhEur: Cellulosi pulvis
USPNF: Powdered cellulose

2 Synonyms

Arbocel; E460; *Elcema*; *Sanacel*; *Solka-Floc*.

3 Chemical Name and CAS Registry Number

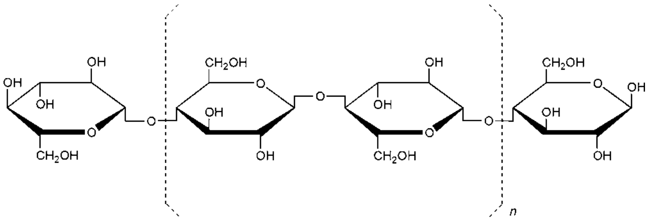
Cellulose [9004-34-6]

4 Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ $\approx 243\,000$ where $n \approx 500$.

Since cellulose is derived from a natural polymer, it has variable chain length and thus variable molecular weight. *See also* Sections 8 and 13.

5 Structural Formula



6 Functional Category

Adsorbent; glidant; suspending agent; tablet and capsule diluent; tablet disintegrant.

7 Applications in Pharmaceutical Formulation or Technology

Powdered cellulose is used as a tablet diluent and a hard gelatin capsule filler; *see* Table I. In both contexts it acts as a bulking agent to increase the physical size of the dosage form for formulations containing a small amount of active substance.

Powdered cellulose has acceptable compression properties, although its flow properties are poor. However, low-crystallinity powdered cellulose has exhibited properties that are different from standard powdered cellulose materials, and has shown potential as a direct-compression excipient.(1)

In soft gelatin capsules, powdered cellulose may be used to reduce the sedimentation rate of oily suspension fills. It is also used as the powder base material of powder dosage forms, and as a suspending agent in aqueous suspensions for peroral delivery. It may also be used to reduce sedimentation during the manufacture of suppositories.

Powdered cellulose has been investigated as an alternative to microcrystalline cellulose as an agent to assist the manufacture of pellets by extrusion/spheronization.(2,3)

Powdered cellulose is also used widely in cosmetics and food products.

Table I: Uses of powdered cellulose.

Use	Concentration (%)
Capsule filler	0–100
Tablet binder	5–25
Tablet disintegrant	5–15
Tablet glidant	1–2

8 Description

Powdered cellulose occurs as a white or almost white, odorless and tasteless powder of various particle sizes, ranging from a free-flowing fine or granular dense powder, to a coarse, fluffy, nonflowing material.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for powdered cellulose.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	+	+	—
Microbial limits			
Aerobic	$\leqslant 10^3$/g	$\leqslant 10^3$/g	$\leqslant 10^3$/g
Fungi and yeast	$\leqslant 10^2$/g	$\leqslant 10^2$/g	$\leqslant 10^2$/g
pH (10% w/w suspension)	5.0–7.5	5.0–7.5	5.0–7.5
Loss on drying	⩽6.0%	⩽6.5%	⩽6.0%
Residue on ignition	⩽0.3%	⩽0.3%	⩽0.3%
Solubility	—	+	—
Ether-soluble substances	⩽15.0 mg	⩽0.15%	⩽0.15%
Water-soluble substances	⩽15.0 mg	⩽1.5%	⩽1.5%
Heavy metals	⩽10 ppm	⩽10 ppm	⩽0.001%
Organic volatile impurities	—	—	+

10 Typical Properties

Angle of repose:
<62° for *Arbocel M80*;
<49° for *Arbocel P 290*;
<36° for *Arbocel A 300* (J. Rettenmaier and Söhne).

Density (bulk): 0.139–0.391 g/cm^3, depending on the source.
Density (tapped): 0.210–0.481 g/cm^3, depending on the source.
Density (true): 1.5 g/cm^3
Moisture content: powdered cellulose is slightly hygroscopic;(4) *see* Figures 1 and 2.
Particle size distribution: powdered cellulose is commercially available in several different particle sizes.

Arbocel M80: average particle size 60 μm;
Arbocel P 290: average particle size 70 μm;
Arbocel A 300: average particle size 200 μm.

Solubility: practically insoluble in water, dilute acids, and most organic solvents although it disperses in most liquids. Slightly soluble in 5% w/v sodium hydroxide solution. Powdered cellulose does not swell in water, but does so in dilute sodium hypochlorite (bleach).

11 Stability and Storage Conditions

Powdered cellulose is a stable, slightly hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatible with strong oxidizing agents.

13 Method of Manufacture

Powdered cellulose is manufactured by the purification and mechanical size reduction of α-cellulose obtained as a pulp from fibrous plant materials.

14 Safety

Powdered cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a nontoxic and nonirritant material.

Powdered cellulose is not absorbed systemically following peroral administration and thus has little toxic potential. Consumption of large quantities of cellulose may, however, have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations.

Deliberate abuse of formulations containing cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas.(5)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Powdered cellulose may be irritant to the eyes. Gloves, eye protection, and a dust mask are recommended. In the UK, the occupational exposure limits for cellulose have been set at 10 mg/m^3 long-term (8-hour TWA) for total inhalable dust and 4 mg/m^3 for respirable dust; the short-term limit for total inhalable dust has been set at 20 mg/m^3.(6)

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Cellulose, microcrystalline.

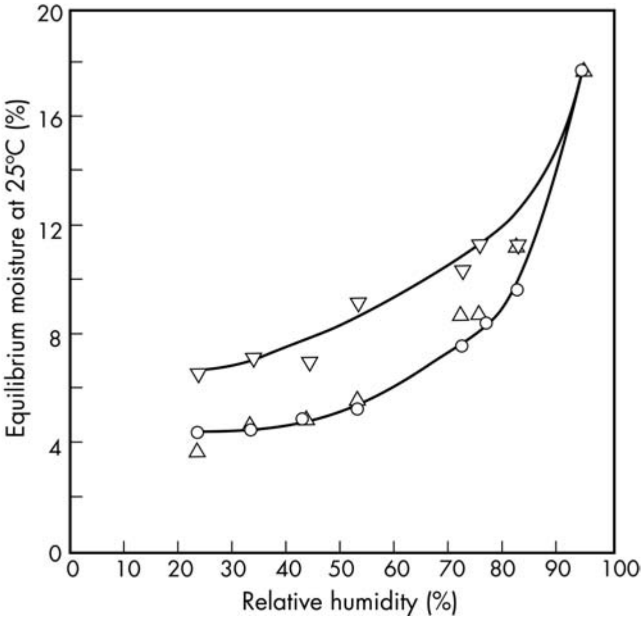


Figure 1: Equilibrium moisture content of powdered cellulose at 25°C.
○: Powdered cellulose (*Solka-Floc BW-40*, Lot no. 8-10-30A)
△: Powdered cellulose (*Solka-Floc BW-20*, Lot no. 22A-19)
▽: Powdered cellulose (*Solka-Floc Fine Granular*, Lot no. 9-10-8)

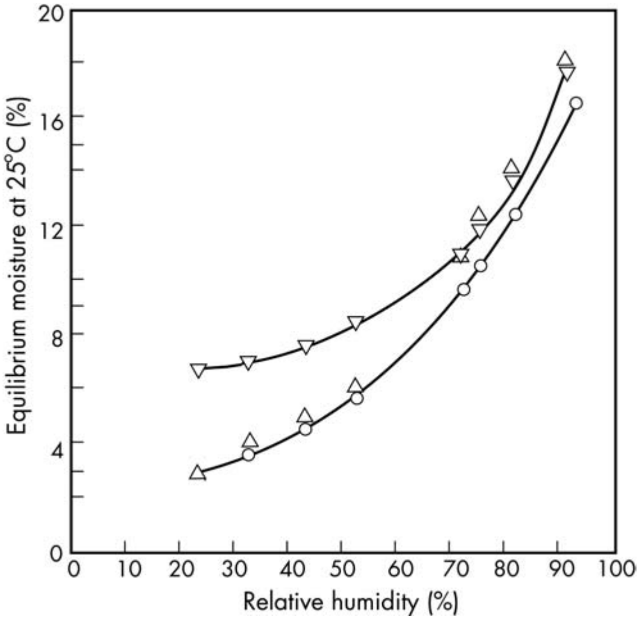


Figure 2: Equilibrium moisture content of powdered cellulose at 25°C.
○: Powdered cellulose (*Solka-Floc BW-100*, Lot no. 9-7-18B)
△: Powdered cellulose (*Solka-Floc BW-200*, Lot no. 22A-20)
▽: Powdered cellulose (*Solka-Floc Fine BW-2030*, Lot no. 240)

18 Comments

A specification for powdered cellulose is contained in the Food Chemicals Codex (FCC).

The EINECS number for powdered cellulose is 232-674-9.

19 Specific References

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See also Cellulose, microcrystalline.

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21 Authors

ME Aulton.

22 Date of Revision

21 August 2005.

Cellulose, Silicified Microcrystalline

1 Nonproprietary Names

None adopted.

2 Synonyms

ProSolv.

3 Chemical Name and CAS Registry Number

See Section 8.

4 Empirical Formula and Molecular Weight

See Section 8.

5 Structural Formula

See Section 8.

6 Functional Category

Tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Silicified microcrystalline cellulose is used as a filler in the formulation of capsules and tablets. It has improved compaction properties in both wet granulation and direct compression compared to conventional microcrystalline cellulose.(1–5) Silicified microcrystalline cellulose was specifically developed to address the loss of compaction that occurs with microcrystalline cellulose after wet granulation.

8 Description

Silicified microcrystalline cellulose is a synergistic, intimate physical mixture of two components: microcrystalline cellulose and colloidal silicon dioxide (for further information *see* Cellulose, Microcrystalline and Colloidal Silicon Dioxide). Silicified microcrystalline cellulose contains 2% w/w colloidal silicon dioxide.

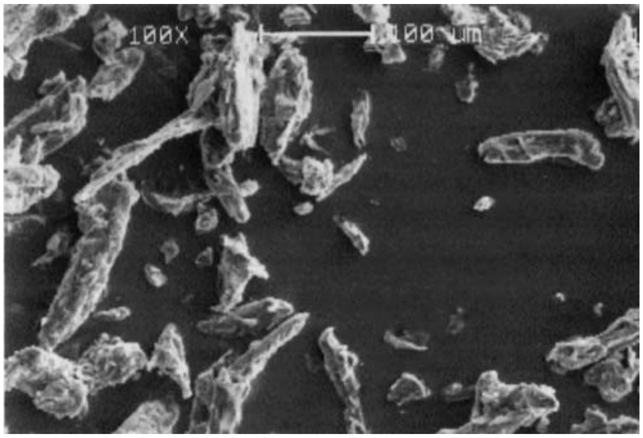
9 Pharmacopeial Specifications

—

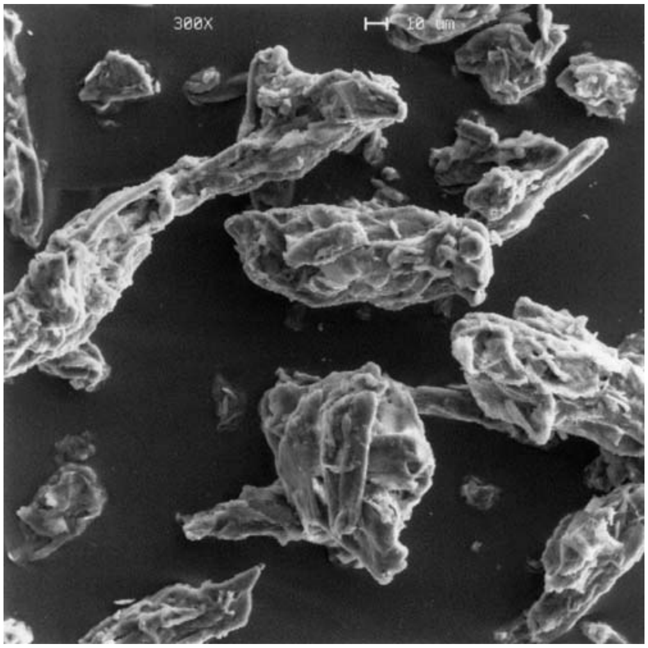
10 Typical properties

Acidity/alkalinity: pH = 5.0–7.5 (10% w/v suspension)
Density: 1.58 g/cm(5)
Density (bulk): 0.31 g/cm^3
Density (tapped): 0.39 g/cm(5)
Melting point: the microcrystalline cellulose component chars at 260–270°C.
Moisture content: typically less than 6% w/w.
Particle size distribution: typical particle size is 20–200 μm. Different grades may have a different normal mean particle size.
Solubility: practically insoluble in water, dilute acids, and most organic solvents. The microcrystalline cellulose component is slightly soluble in 5% w/w sodium hydroxide solution.

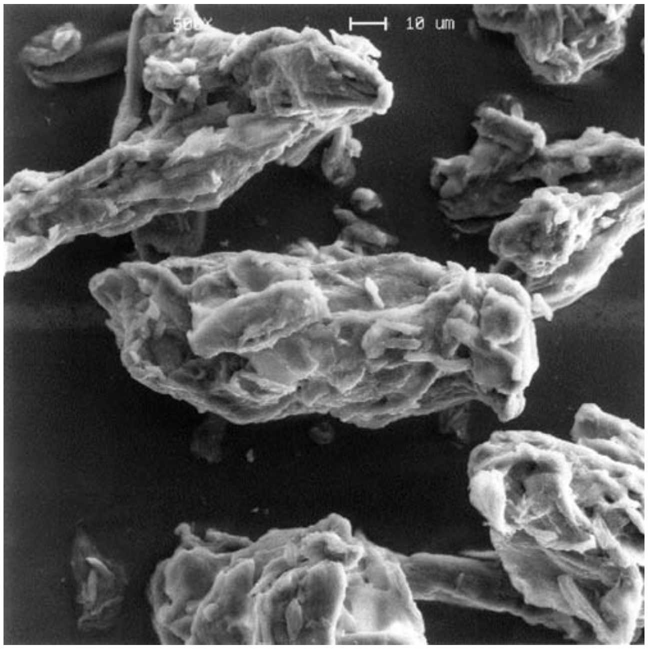
SEM: 1
Excipient: Silicified microcrystalline cellulose
Manufacturer: JRS Pharma LP
Lot No.: CSD5866
Magnification: 100×



SEM: 2
Excipient: Silicified microcrystalline cellulose
Manufacturer: JRS Pharma LP
Lot No.: CSD5866
Magnification: 300×



SEM: 3
Excipient: Silicified microcrystalline cellulose
Manufacturer: JRS Pharma LP
Lot No.: CSD5866
Magnification: 500×



11 Stability and Storage Conditions

Silicified microcrystalline cellulose is stable when stored in a well-closed container in a cool, dry place.

12 Incompatibilities

See Cellulose, Microcrystalline and Colloidal Silicon Dioxide.

13 Method of Manufacture

Silicified microcrystalline cellulose is manufactured by co-drying a suspension of microcrystalline cellulose particles and colloidal silicon dioxide so that the dried finished product contains 2% w/w colloidal silicon dioxide.

The colloidal silicon dioxide appears physically bound onto the surface and inside the silicified microcrystalline cellulose particles. Extensive studies using different spectroscopic methods have failed to show any form of chemical interaction.(4,6,7)

14 Safety

See Cellulose, Microcrystalline and Colloidal Silicon Dioxide.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Handling of silicified microcrystalline cellulose can generate nuisance dusts and the use of a respirator or dust mask may be necessary.

Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection, and a dust mask are recommended. In the UK the long-term occupational exposure limits (8-hour TWA) have been set at 10 mg/m^3 for total inhalable dust and 4 mg/m^3 for respirable dust; short-term limit for total inhalable dust has been set at 20 mg/m^3.(8)

Since the colloidal silicon dioxide is physically bound to the microcrystalline cellulose the general recommendations of gloves, eye protection, and a dust mask should be followed when handling silicified microcrystalline cellulose.

16 Regulatory Status

Silicified microcrystalline cellulose is a physical mixture of two materials both of which are generally regarded as nontoxic:

Microcrystalline cellulose: GRAS listed. Included in the FDA Inactive Ingredients Guide (inhalations, oral capsules, powders, suspensions, syrups, and tablets). Included in nonparenteral medicines licensed in Europe and the US. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

Colloidal silicon dioxide: GRAS listed. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in Europe and the US. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Cellulose, microcrystalline; colloidal silicon dioxide.

18 Comments

Silicified microcrystalline cellulose has greater tensile strength and requires lower compression pressures than regular grades of microcrystalline cellulose. Furthermore, silicified microcrystalline cellulose maintains its compactability when wet granulated; the compacts exhibit greater stiffness and they require considerably more energy for tensile failure to occur.(4,9)

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21 Authors

RC Moreton.

22 Date of Revision

26 August 2005.

Cellulose Acetate

1 Nonproprietary Names

BP: Cellulose acetate
PhEur: Cellulosi acetas
USPNF: Cellulose acetate

2 Synonyms

Acetyl cellulose; cellulose diacetate; cellulose triacetate.

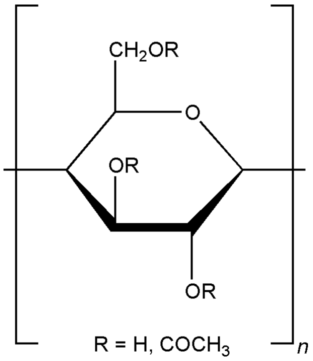
3 Chemical Name and CAS Registry Number

Cellulose acetate [9004-35-7]
Cellulose diacetate [9035-69-2]
Cellulose triacetate [9012-09-3]

4 Empirical Formula and Molecular Weight

Cellulose acetate is cellulose in which a portion or all of the hydroxyl groups are acetylated. Cellulose acetate is available in a wide range of acetyl levels and chain lengths and thus molecular weights; *see* Table I.

5 Structural Formula



6 Functional Category

Coating agent; extended release agent; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Cellulose acetate is widely used in pharmaceutical formulations both in sustained-release applications and for taste masking.

Cellulose acetate is used as a semipermeable coating on tablets, especially on osmotic pump-type tablets and implants. This allows for controlled, extended release of actives.(1–5) Cellulose acetate films, in conjunction with other materials, also offer sustained release without the necessity of drilling a hole in the coating as is typical with osmotic pump systems. Cellulose acetate and other cellulose esters have also been used to form drug-loaded microparticles with controlled-release characteristics.(6,7)

Cellulose acetate films are used in transdermal drug delivery systems(8,9) and also as film coatings on tablets or granules for taste masking. For example, acetaminophen granules have been coated with a cellulose acetate-based coating before being processed to provide chewable tablets. Extended-release tablets can also be formulated with cellulose acetate as a directly compressible matrix former.(10) The release profile can be modified by changing the ratio of active to cellulose acetate and by incorporation of plasticizer, but was shown to be insensitive to cellulose acetate molecular weight and particle size distribution.

Therapeutically, cellulose acetate has been used to treat cerebral aneurysms, and also for spinal perimedullary arteriovenous fistulas.(11)

8 Description

Cellulose acetate occurs as a white to off-white powder, free-flowing pellets, or flakes. It is tasteless and odorless, or may have a slight odor of acetic acid.

Table I: Comparison of different types of cellulose acetate.[2]

Type	Acetyl (%)	Viscosity (mPa s)	Hydroxyl (%)	Melting range (°C)	T_g[a] (°C)	Density[b] (g/cm^3)	MWn[c]
CA-320S	32.0	210.0	8.7	230–250	180	0.4	38 000
CA-398-3	39.8	11.4	3.5	230–250	180	0.4	30 000
CA-398-6	39.8	22.8	3.5	230–250	182	0.4	35 000
CA-398-10NF	39.8	38.0	3.5	230–250	185	0.4	40 000
CA-398-30	39.7	114.0	3.5	230–250	189	0.4	50 000
CA-394-60S	39.5	228.0	4.0	240–260	186	—	60 000
CA-435-75	43.5	—	0.9	280–300	185	0.7	122 000

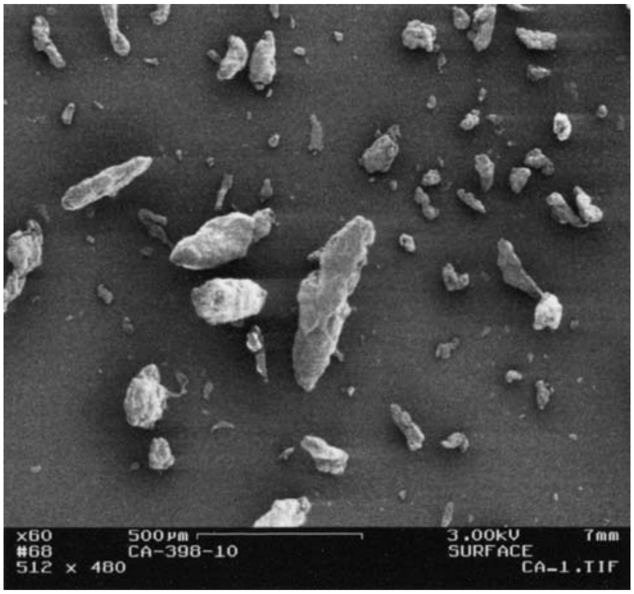
[a] Glass transition temperature.

[b] Tapped.

[c] Number average molecular weight in polystyrene equivalents.

Supplier: Eastman Chemical Company.

SEM: 1
Excipient: Cellulose acetate, CA-398-10NF
Manufacturer: Eastman Chemical Co.
Lot No.: AC65280NF
Magnification: 60×
Voltage: 3 kV



9 Pharmacopeial Specifications

See Table II.

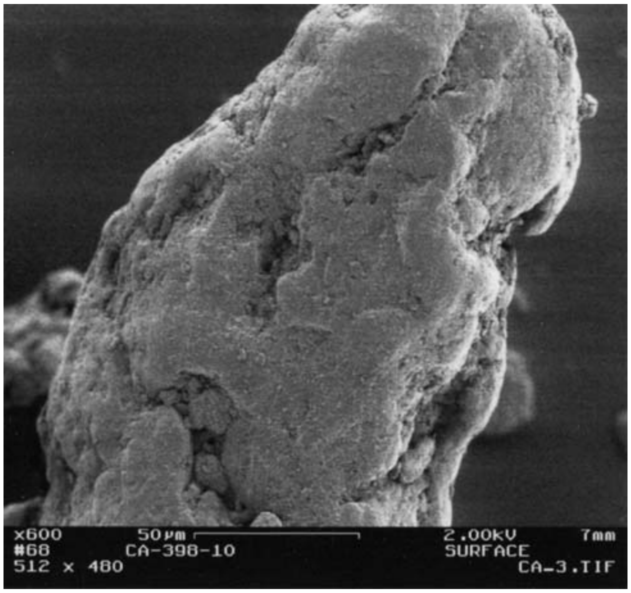
Table II: Pharmacopeial specifications for cellulose acetate.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Loss on drying	$\leqslant 5.0\%$	$\leqslant 5.0\%$
Residue on ignition	$\leqslant 0.1\%$	$\leqslant 0.1\%$
Free acid	$\leqslant 0.1\%$	$\leqslant 0.1\%$
Heavy metals	$\leqslant 10$ ppm	$\leqslant 0.001\%$
Microbial contamination	+	—
Aerobic	$\leqslant 10^3$/g	—
Fungi and yeast	$\leqslant 10^2$/g	—
Organic volatile impurities	—	+
Assay (of acetyl groups)	29.0–44.8%	29.0–44.8%

10 Typical Properties

Density (bulk): typically 0.4 g/cm^3 for powders
Glass transition temperature: 170–190°C
Melting point: melting range 230–300°C
Solubility: the solubility of cellulose acetate is greatly influenced by the level of acetyl groups present. In general, cellulose acetates are soluble in acetone–water blends of varying ratios, dichloromethane–ethanol blends, dimethyl formamide, and dioxane. The cellulose acetates of higher acetyl level are generally more limited in solvent choice than are the lower-acetyl materials.
Viscosity (dynamic): various grades of cellulose acetate are commercially available that differ in their acetyl content and degree of polymerization. They can be used to produce 10% w/v solutions in organic solvents with viscosities of 10–230 mPa s. Blends of cellulose acetates may also be prepared with intermediate viscosity values. *See also* Table I.

SEM 2
Excipient: Cellulose acetate, CA-398-10NF
Manufacturer: Eastman Chemical Co.
Lot No.: AC65280NF
Magnification: 600×
Voltage: 2 kV



11 Stability and Storage Conditions

Cellulose acetate is stable if stored in a well-closed container in a cool, dry place. Cellulose acetate hydrolyzes slowly under prolonged adverse conditions such as high temperature and humidity, with a resultant increase in free acid content and odor of acetic acid.

12 Incompatibilities

Cellulose acetate is incompatible with strongly acidic or alkaline substances. Cellulose acetate is compatible with the following plasticizers: diethyl phthalate, polyethylene glycol, triacetin, and triethyl citrate.

13 Method of Manufacture

Cellulose acetate is prepared from highly purified cellulose by treatment with acid catalysis and acetic anhydride.

14 Safety

Cellulose acetate is widely used in oral pharmaceutical products and is generally regarded as a nontoxic and nonirritant material.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Dust may be irritant to the eyes and eye protection should be worn. Like most organic materials in powder form, these materials are capable of creating dust explosions. Cellulose acetate is combustible.

16 Regulatory Acceptance

Included in the FDA Inactive Ingredients Guide (oral tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Cellulose acetate phthalate.

18 Comments

When solutions are being prepared, cellulose acetate should always be added to the solvent, not the reverse. Various grades of cellulose acetate are available with varying physical properties; *see* Table I.

19 Specific References

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20 General References

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21 Authors

LA Miller.

22 Date of Revision

15 August 2005.

Cellulose Acetate Phthalate

1 Nonproprietary Names

BP: Cellacefate
JP: Cellulose acetate phthalate
PhEur: Cellulosi acetas phthalas
USPNF: Cellacefate

2 Synonyms

Acetyl phthalyl cellulose; *Aquacoat cPD*; CAP; cellacephate; cellulose acetate benzene-1,2-dicarboxylate; cellulose acetate hydrogen 1,2-benzenedicarboxylate; cellulose acetate hydrogen phthalate; cellulose acetate monophthalate; cellulose acetophthalate; cellulose acetylphthalate.

3 Chemical Name and CAS Registry Number

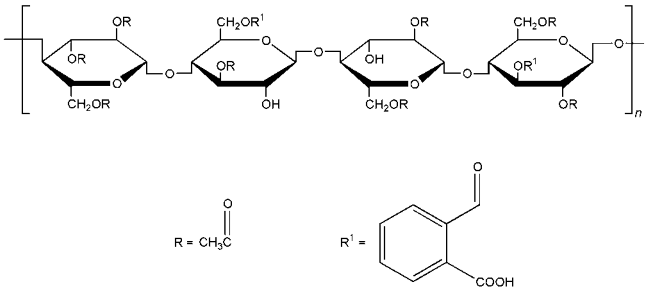
Cellulose, acetate, 1,2-benzenedicarboxylate [9004-38-0]

4 Empirical Formula and Molecular Weight

Cellulose acetate phthalate is a cellulose in which about half the hydroxyl groups are acetylated, and about a quarter are esterified with one of two acid groups being phthalic acid, where the remaining acid group is free. *See* Section 5.

5 Structural Formula

The PhEur 2005 and USPNF 23 describe cellulose acetate phthalate as a reaction product of phthalic anhydride and a partial acetate ester of cellulose containing 21.5–26.0% of acetyl (C_2H_3O) groups, and 30.0–36.0% of phthalyl(*o*-carboxybenzoyl, $C_8H_5O_3$) groups.



6 Functional Category

Coating agent.

7 Applications in Pharmaceutical Formulation or Technology

Cellulose acetate phthalate (CAP) is used as an enteric film coating material, or as a matrix binder for tablets and capsules.(1–8) Such coatings resist prolonged contact with the strongly acidic gastric fluid, but dissolve in the mildly acidic or neutral intestinal environment.

Cellulose acetate phthalate is commonly applied to solid-dosage forms either by coating from organic or aqueous solvent systems or by direct compression. Concentrations generally used are 0.5–9.0% of the core weight. The addition of plasticizers improves the water resistance of this coating material, and formulations using such plasticizers are more effective than when cellulose acetate phthalate is used alone.

Cellulose acetate phthalate is compatible with many plasticizers, including acetylated monoglyceride; butyl phthalylbutyl glycolate; dibutyl tartrate; diethyl phthalate; dimethyl phthalate; ethyl phthalylethyl glycolate; glycerin; propylene glycol; triacetin; triacetin citrate; and tripropionin. It is also used in combination with other coating agents such as ethyl cellulose, in drug controlled-release preparations.

Therapeutically, cellulose acetate phthalate has recently been reported to exhibit experimental microbicidal activity against sexually transmitted disease pathogens, such as the HIV-1 retrovirus.(9,10)

8 Description

Cellulose acetate phthalate is a hygroscopic, white to off-white, free-flowing powder, granule, or flake. It is tasteless and odorless, or might have a slight odor of acetic acid.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for cellulose acetate phthalate.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	+	+	—
Free acid	⩽3.0%	⩽3.0%	⩽3.0%
Heavy metals	⩽10 ppm	⩽10 ppm	⩽0.001%
Organic volatile impurities	—	—	+
Phthaloyl groups	—	+	+
Residue on ignition	⩽0.1%	⩽0.1%	⩽0.1%
Viscosity (15% w/v solution)	45–90 mPa s	45.0–90.0 mPa s	45.0–90.0 mPa s
Water	⩽5.0%	⩽5.0%	⩽5.0%
Assay	+	+	+
Acetyl groups	21.5–26.0%	21.5–26.0%	21.5–26.0%
Carboxybenzoyl groups	30.0–40.0%	30.0–36.0%	30.0–36.0%

10 Typical Properties

Density (bulk): 0.260 g/cm^3
Density (tapped): 0.266 g/cm^3
Melting point: 192°C. Glass transition temperature is 160–170°C.(11)
Moisture content: 2.2%. Cellulose acetate phthalate is hygroscopic and precautions are necessary to avoid excessive absorption of moisture.(12) *See also* Figure 1.

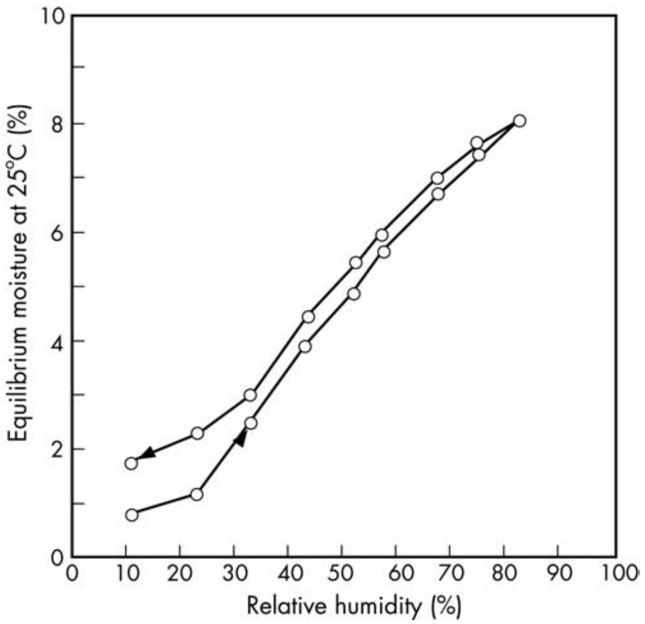


Figure 1: Sorption–desorption isotherm of cellulose acetate phthlate.

Table II: Examples of solvents with which cellulose acetate phthalate has ⩽10% w/w solubility.

Acetone
Diacetone alcohol
Dioxane
Ethoxyethyl acetate
Ethyl glycol monoacetate
Ethyl lactate
Methoxyethyl acetate
β-Methoxyethylene alcohol
Methyl acetate
Methyl ethyl ketone

Table III: Examples of solvent mixtures with which cellulose acetate phthalate has ⩽10% w/w solubility.

Acetone : ethanol (1 : 1)
Acetone : water (97 : 3)
Benzene : methanol (1 : 1)
Ethyl acetate : ethanol (1 : 1)
Methylene chloride : ethanol (3 : 1)

Solubility: practically insoluble in water, alcohols, and chlorinated and nonchlorinated hydrocarbons. Soluble in a number of ketones, esters, ether alcohols, cyclic ethers, and in certain solvent mixtures. It can be soluble in certain buffered aqueous solutions as low as pH 6.0. Cellulose acetate phthalate has a solubility of ⩽10% w/w in a wide range of solvents and solvent mixtures; *see* Table II and Table III.

Viscosity (dynamic): a 15% w/w solution in acetone with a moisture content of 0.4% has a viscosity of 50–90 mPa s (50–90 cP). This is a good coating solution with a honey-like consistency, but the viscosity is influenced by the purity of the solvent.

11 Stability and Storage Conditions

Slow hydrolysis of cellulose acetate phthalate will occur under prolonged adverse conditions such as high temperatures and high humidity, with a resultant increase in free acid content, viscosity, and odor of acetic acid. However, cellulose acetate phthalate is stable if stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Cellulose acetate phthalate is incompatible with ferrous sulfate, ferric chloride, silver nitrate, sodium citrate, aluminum sulfate, calcium chloride, mercuric chloride, barium nitrate, basic lead acetate, and strong oxidizing agents such as strong alkalis and acids.

13 Method of Manufacture

Cellulose acetate phthalate is produced by reacting the partial acetate ester of cellulose with phthalic anhydride in the presence of a tertiary organic base such as pyridine, or a strong acid such as sulfuric acid.

14 Safety

Cellulose acetate phthalate is widely used in oral pharmaceutical products and is generally regarded as a nontoxic material, free of adverse effects.

Results of long-term feeding in rats and dogs have indicated a low oral toxicity. Rats survived daily feedings of up to 30% in the diet for up to 1 year without showing a depression in growth. Dogs fed 16 g daily in the diet for 1 year remained normal.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Cellulose acetate phthalate may be irritant to the eyes, mucous membranes, and upper respiratory tract. Eye protection and gloves are recommended. Cellulose acetate phthalate should be handled in a well-ventilated environment; use of a respirator is recommended when handling large quantities.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Cellulose acetate; hypromellose phthalate; polyvinyl acetate phthalate.

18 Comments

Any plasticizers that are used with cellulose acetate phthalate to improve performance should be chosen on the basis of experimental evidence. The same plasticizer used in a different tablet base coating may not yield a satisfactory product.

In using mixed solvents, it is important to dissolve the cellulose acetate phthalate in the solvent with the greater dissolving power, and then to add the second solvent. Cellulose acetate phthalate should always be added to the solvent, not the reverse.

Cellulose acetate phthalate films are permeable to certain ionic substances, such as potassium iodide and ammonium chloride. In such cases, an appropriate sealer subcoat should be used.

A reconstituted colloidal dispersion of latex particles rather than solvent solution coating material of cellulose acetate phthalate is also available. This white, water-insoluble powder is composed of solid or semisolid submicrometer-sized polymer spheres with an average particle size of 0.2 μm. A typical coating system made from this latex powder is a 10–30% solid-content aqueous dispersion with a viscosity in the 50–100 mPa s range.

19 Specific References

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21 Authors

LA Miller.

22 Date of Revision

15 August 2005.

Ceratonia

1 Nonproprietary Names

None adopted.

2 Synonyms

Algaroba; carob bean gum; carob flour; ceratonia gum; ceratonia siliqua; ceratonia siliqua gum; Cheshire gum; E410; gomme de caroube; locust bean gum; *Meyprofleur*; St. John's bread.

3 Chemical Name and CAS Registry Number

Carob gum [9000-40-2]

4 Empirical Formula and Molecular Weight

Ceratonia is a naturally occurring plant material that consists chiefly of a high molecular weight hydrocolloidal polysaccharide, composed of D-galactose and D-mannose units combined through glycosidic linkages, which may be described chemically as galactomannan. The molecular weight is approximately 310 000.

5 Structural Formula

See Section 4.

6 Functional Category

Controlled-release vehicle; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Ceratonia is a naturally occurring material generally used as a substitute for tragacanth or other similar gums. A ceratonia mucilage that is slightly more viscous than tragacanth mucilage may be prepared by boiling 1.0–1.5% of powdered ceratonia with water. As a viscosity-increasing agent, ceratonia is said to be five times as effective as starch and twice as effective as tragacanth. Ceratonia has also been used as a tablet binder(1) and is used in oral controlled-release drug delivery systems approved in Europe and the USA.

Ceratonia is widely used as a binder, thickening agent, and stabilizing agent in the cosmetics and food industry. In foods, 0.15–0.75% is used. Therapeutically, ceratonia mucilage is used orally in adults and children to regulate intestinal function; *see* Section 14.

8 Description

Ceratonia occurs as a yellow-green or white colored powder. Although odorless and tasteless in the dry powder form, ceratonia acquires a leguminous taste when boiled in water.

9 Pharmacopeial Specifications

See Section 18.

10 Typical Properties

Acidity/alkalinity: pH = 5.3 (1% w/v aqueous solution)

Solubility: ceratonia is dispersible in hot water, forming a sol having a pH 5.4–7.0 that may be converted to a gel by the addition of small amounts of sodium borate. In cold water, ceratonia hydrates very slowly and incompletely. Ceratonia is practically insoluble in ethanol.

Viscosity (dynamic): 1200–2500 mPa s (1200–2500 cP) for a 1% w/v aqueous dispersion at 25°C. Viscosity is unaffected by pH within the range pH 3–11. Viscosity is increased by heating: if heated to 95°C then cooled, practically clear solutions may be obtained that are more viscous than prior to heating.

11 Stability and Storage Conditions

The bulk material should be stored in a well-closed container in a cool, dry place. Ceratonia loses not more than 15% of its weight on drying.

12 Incompatibilities

The viscosity of xanthan gum solutions is increased in the presence of ceratonia.(2) This interaction is used synergistically in controlled-release drug delivery systems.

13 Method of Manufacture

Ceratonia is a naturally occurring material obtained from the ground endosperms separated from the seeds of the locust bean tree, *Ceratonia siliqua* (Leguminosae). The tree is indigenous to southern Europe and the Mediterranean region.

14 Safety

Ceratonia is generally regarded as an essentially noncarcinogenic,(3) nontoxic and nonirritant material. Therapeutically, it has been used in oral formulations for the control of vomiting and diarrhea in adults and children; 20–40 g daily in adults has been used dispersed in liquid.(4) As an excipient, ceratonia is used in oral controlled-release formulations approved in Europe and the USA.

Ceratonia is also widely used in food products. The WHO has not specified an acceptable total daily intake for ceratonia as the total daily intake arising from its use at the levels necessary to achieve the desired effect, and from its acceptable background in food, was not considered to represent a hazard to health.(5) Ceratonia hypersensitivity has been reported, in a single case report, in an infant.(6) However, ceratonia is said to be nonallergenic in children with known allergy to peanuts.(7)

LD_{50} (hamster, oral): 10.0 g/kg(8)
LD_{50} (mouse, oral): 13.0 g/kg
LD_{50} (rabbit, oral): 9.1 g/kg
LD_{50} (rat, oral): 13.0 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. When heated to decomposition ceratonia emits acrid smoke and irritating fumes.

16 Regulatory Status

GRAS listed. Accepted for use in Europe as a food additive. In Europe and the USA, ceratonia has been used in oral tablet formulations.

17 Related Substances

Acacia; ceratonia extract; tragacanth; xanthan gum.

Ceratonia extract

Synonyms: ceratonia siliqua extract; extract of carob; locust tree extract.

CAS number: [84961-45-5]

Comments: ceratonia extract is used as an emollient. The EINECS number for ceratonia extract is 284-634-5.

18 Comments

The EINECS number for ceratonia is 232-541-5.

Although not included in any pharmacopeias, a specification for ceratonia is contained in the Food Chemicals Codex (FCC), *see* Table I.(9) However, ceratonia (locust bean gum) is described under reagent specifications in the USP 28, where the reader is directed to the FCC specifications. Ceratonia (carob bean gum) is mentioned in the BP 2004 under general reagents and is described as a white powder containing 70–80% of a water-soluble gum consisting mainly of galactomannoglycone.

Table I: Food Chemicals Codex specifications for ceratonia.(9)

Test	FCC 1996
Identification	+
Acid-insoluble matter	≤4.0%
Arsenic	≤3 mg/kg
Ash	≤1.2%
Galactomannans	≥75%
Heavy metals (as Pb)	≤0.002%
Lead	≤5 mg/kg
Loss on drying	≤14.0%
Protein	≤7.0%
Starch	+

19 Specific References

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21 Authors

PJ Weller.

22 Date of Revision

14 August 2005.

Cetostearyl Alcohol

1 Nonproprietary Names

BP: Cetostearyl alcohol
PhEur: Alcohol cetylicus et stearylicus
USPNF: Cetostearyl alcohol

2 Synonyms

Cetearyl alcohol; *Crodacol CS90*; *Lanette O*; *Tego Alkanol 1618*; *Tego Alkanol 6855*.

3 Chemical Name and CAS Registry Number

Cetostearyl alcohol [67762-27-0] and [8005-44-5]

4 Empirical Formula and Molecular Weight

Cetostearyl alcohol is a mixture of solid aliphatic alcohols consisting mainly of stearyl ($C_{18}H_{38}O$) and cetyl ($C_{16}H_{34}O$) alcohols. The proportion of stearyl to cetyl alcohol varies considerably, but the material usually consists of about 50–70% stearyl alcohol and 20–35% cetyl alcohol, with limits specified in pharmacopeias. The combined stearyl alcohol and cetyl alcohol comprise at least 90% of the material. Small quantities of other alcohols, chiefly myristyl alcohol, make up the remainder of the material. Two emulsifying grades of ceteostearyl alcohol are recognized by the PhEur 2005 and contain at least 7% surfactant, with Type A containing sodium cetostearyl sulfate and Type B containing sodium lauryl sulfate.

5 Structural Formula

See Section 4.

6 Functional Category

Emollient; emulsifying agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Cetostearyl alcohol is used in cosmetics and topical pharmaceutical preparations. In topical pharmaceutical formulations, cetostearyl alcohol will increase the viscosity and impart body in both water-in-oil and oil-in-water emulsions. Cetostearyl alcohol will stablize an emulsion and also act as a co-emulsifier, thus decreasing the amount of surfactant required to form a stable emulsion. Cetostearyl alcohol is also used in the preparation of nonaqueous creams and sticks. Research articles have been published in which cetostearyl alcohol has been used to slow the dissolution of water-soluble drugs.(1–4) In combination with surfactants, cetostearyl alcohol forms emulsions with very complex microstructures. These microstructures can include liquid crystals, lamellar structures, and gel phases.(5–16)

8 Description

Cetostearyl alcohol occurs as white or cream-colored unctuous masses, or almost white flakes or granules. It has a faint, characteristic sweet odor. On heating, cetostearyl alcohol melts to a clear, colorless or pale yellow-colored liquid free of suspended matter.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for cetostearyl alcohol.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Melting range	49–56°C	48–55°C
Acid value	≤1.0	≤2.0
Iodine value	≤2.0	≤4
Hydroxyl value	208–228	208–228
Saponification value	≤2.0	—
Assay		
of $C_{18}H_{38}O$	≥40.0%	≥40.0%
of $C_{16}H_{34}O$ and $C_{18}H_{38}O$	≥90.0%	≥90.0%

10 Typical Properties

Solubility: soluble in ethanol (95%), ether, and oil; practically insoluble in water.

11 Stability and Storage Conditions

Cetostearyl alcohol is stable under normal storage conditions. Cetostearyl alcohol should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatible with strong oxidizing agents and metal salts.

13 Method of Manufacture

Cetostearyl alcohol is prepared by the reduction of the appropriate fatty acids from vegetable and animal sources. Cetostearyl alcohol can also be prepared directly from hydrocarbon sources.

14 Safety

Cetostearyl alcohol is mainly used in topical pharmaceutical formulations and topical cosmetic formulations.

Cetostearyl alcohol is generally regarded as a nontoxic material.(17) Although it is essentially nonirritating, sensitization reactions to cetostearyl, cetyl, and stearyl alcohols(18–23) have been reported.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Cetostearyl alcohol is flammable and on combustion may produce fumes containing carbon monoxide.

16 Regulatory Status

Accepted as an indirect food additive and as an adhesive and a component of packaging coatings in the USA. Included in the FDA Inactive Ingredients Guide (oral tablets and topical emulsions, lotions, ointments, vaginal suppositories). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Anionic emulsifying wax; cetyl alcohol; sodium lauryl sulfate; stearyl alcohol.

18 Comments

The composition of cetostearyl alcohol from different sources may vary considerably. The composition of the minor components, typically straight-chain and branched-chain alcohols, varies greatly depending upon the source, which may be animal, vegetable, or synthetic. This has been reported in the literature to impart differences in emulsification behavior, particularly with respect to emulsion consistency or stability.(14–16)

The PhEur 2005 also contains specifications for cetostearyl alcohol, emulsifying Type A, and Type B, respectively.

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22 Date of Revision

12 August 2005.

Cetrimide

1 Nonproprietary Names

BP: Cetrimide
PhEur: Cetrimidum

2 Synonyms

Bromat; *Cetab*; *Cetavlon*; *Cetraol*; *Lissolamine V*; *Micol*; *Morpan CHSA*; *Morphans*; *Quammonium*; *Sucticide*.

3 Chemical Name and CAS Registry Number

Cetrimide [8044-71-1]

Note that the above name, CAS Registry Number, and synonyms refer to the PhEur 2005 material which, although it consists predominantly of trimethyltetradecylammonium bromide, may also contain other bromides; *see* Section 4.

There is some confusion in the literature regarding the synonyms, CAS Registry Number, and molecular weight applied to cetrimide. It is most common to find the molecular weight and CAS Registry Number of trimethyltetradecylammonium bromide used, as this is the principal component of cetrimide. It should be noted however, that in the original BP 1953 material the principal component of cetrimide was hexadecyltrimethylammonium bromide.

The CAS Registry Number for hexadecyltrimethylammonium hydroxide [505-86-2] has also been widely applied to cetrimide.

See Section 17 for further information.

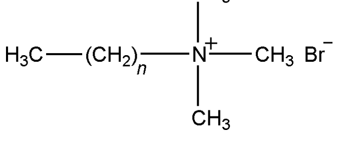
4 Empirical Formula and Molecular Weight

Cetrimide consists mainly of trimethyltetradecylammonium bromide ($C_{17}H_{38}BrN$), and may contain smaller amounts of dodecyltrimethylammonium bromide ($C_{15}H_{34}BrN$) and hexadecyltrimethylammonium bromide ($C_{19}H_{42}BrN$).

$C_{17}H_{38}BrN$ 336.40

See also Section 17.

5 Structural Formula



$H_3C—(CH_2)_n—N^+(CH_3)_3\ Br^-$

where
n = 11 for dodecyltrimethylammonium bromide
n = 13 for trimethyltetradecylammonium bromide
n = 15 for hexadecyltrimethylammonium bromide

6 Functional Category

Antimicrobial preservative; antiseptic; cationic surfactant; disinfectant.

7 Applications in Pharmaceutical Formulation or Technology

Cetrimide is a quaternary ammonium compound that is used in cosmetics and pharmaceutical formulations as an antimicrobial preservative; *see* Section 10. It may also be used as a cationic surfactant. In eye-drops, it is used as a preservative at a concentration of 0.005% w/v.

Therapeutically, cetrimide is used in relatively high concentrations, generally as 0.1–1.0% w/v aqueous solutions, as a topical antiseptic for skin, burns, and wounds. Solutions containing 1–3% w/v cetrimide are used as shampoos to remove the scales in seborrhea.

Cetrimide is also used as a cleanser and disinfectant for hard contact lenses, although it should not be used on soft lenses; as an ingredient of cetrimide emulsifying wax, and in o/w creams (e.g. cetrimide cream).

8 Description

Cetrimide is a white to creamy white, free-flowing powder, with a faint but characteristic odor and a bitter, soapy taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for cetrimide.

Test	PhEur 2005
Identification	+
Characters	+
Acidity or alkalinity	+
Appearance of solution	+
Amines and amine salts	+
Loss on drying	$\leqslant$2.0%
Sulfated ash	$\leqslant$0.5%
Assay (as $C_{17}H_{38}BrN$, dried basis)	96.0–101.0%

10 Typical Properties

Acidity/alkalinity: pH = 5.0–7.5 (1% w/v aqueous solution)

Antimicrobial activity: cetrimide has good bactericidal activity against Gram-positive species but is less active against Gram-negative species. *Pseudomonas* species, particularly *Pseudomonas aeruginosa*, may exhibit resistance. Cetrimide is most effective at neutral or slightly alkaline pH values, with activity appreciably reduced in acidic media and in the presence of organic matter. The activity of cetrimide is enhanced in the presence of alcohols. Cetrimide has variable antifungal activity, is effective against some viruses, and is inactive against bacterial spores. Typical minimum inhibitory concentrations (MICs) are shown in Table II.

Table II: Minimum inhibitory concentrations (MIC) of cetrimide.

Microorganism	MIC (μg/mL)
Escherichia coli	30
Pseudomonas aeruginosa	300
Staphylococcus aureus	10

Critical micelle concentration: ≈0.01%

Melting point: 232–247°C

Moisture content: at 40–50% relative humidity and 20°C, cetrimide absorbs sufficient moisture to cause caking and retard flow properties.

Partition coefficients:

Liquid paraffin : water = <1;
Vegetable oil : water = <1.

Solubility: freely soluble in chloroform, ethanol (95%), and water; practically insoluble in ether. A 2% w/v aqueous solution foams strongly on shaking.

11 Stability and Storage Conditions

Cetrimide is chemically stable in the dry state, and also in aqueous solution at ambient temperatures. Aqueous solutions may be sterilized by autoclaving. Water containing metal ions and organic matter may reduce the antimicrobial activity of cetrimide.

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatible with soaps, anionic surfactants, high concentrations of nonionic surfactants, bentonite, iodine, phenylmercuric nitrate, alkali hydroxides, and acid dyes. Aqueous solutions react with metals.

13 Method of Manufacture

Cetrimide is prepared by the condensation of suitable alkyl bromides and trimethylamine.

14 Safety

Most adverse effects reported relate to the therapeutic use of cetrimide. If ingested orally, cetrimide and other quaternary ammonium compounds can cause nausea, vomiting, muscle paralysis, CNS depression, and hypotension; concentrated solutions may cause esophageal damage and necrosis. The fatal oral human dose is estimated to be 1.0–3.0 g.(1)

At the concentrations used topically, solutions do not generally cause irritation, although concentrated solutions have occasionally been reported to cause burns. Cases of hypersensitivity have been reported following repeated application.(2)

Adverse effects that have been reported following irrigation of hydatid cysts with cetrimide solution include chemical peritonitis,(3) methemoglobinemia with cyanosis,(4) and metabolic disorders.(5)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Cetrimide powder and concentrated cetrimide solutions are irritant; avoid inhalation, ingestion, and skin and eye contact. Eye protection, gloves, and a respirator are recommended.(6)

16 Regulatory Status

Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Benzalkonium chloride; benzethonium chloride; dodecyltrimethylammonium bromide; hexadecyltrimethylammonium bromide; trimethyltetradecylammonium bromide.

Dodecyltrimethylammonium bromide

Empirical formula: $C_{15}H_{34}BrN$

Molecular weight: 308.35

CAS number: [1119-94-4]

Synonyms: DTAB; *N*-lauryl-*N*,*N*,*N*-trimethylammonium bromide; *N*,*N*,*N*-trimethyldodecylammonium bromide.

Safety:

LD_{50} (mouse, IV): 5.2 mg/kg(7)
LD_{50} (rat, IV): 6.8 mg/kg

Hexadecyltrimethylammonium bromide

Empirical formula: $C_{19}H_{42}BrN$

Molecular weight: 364.48

CAS number: [57-09-0]

Synonyms: cetrimide BP 1953; cetrimonium bromide; cetyltrimethylammonium bromide; CTAB; *N*,*N*,*N*-trimethylhexadecylammonium bromide.

Appearance: a white to creamy-white, voluminous, free-flowing powder, with a characteristic faint odor and bitter, soapy taste.

Melting point: 237–243°C

Safety:

LD_{50} (guinea pig, SC): 100 mg/kg(8)
LD_{50} (mouse, IP): 106 mg/kg
LD_{50} (mouse, IV): 32 mg/kg
LD_{50} (rabbit, IP): 125 mg/kg
LD_{50} (rabbit, SC): 125 mg/kg
LD_{50} (rat, IV): 44 mg/kg
LD_{50} (rat, oral): 410 mg/kg

Solubility: freely soluble in ethanol (95%); soluble 1 in 10 parts of water.

Comments: the original cetrimide BP 1953 consisted largely of hexadecyltrimethylammonium bromide, with smaller amounts of analogous alkyltrimethylammonium bromides. It contained a considerable proportion of inorganic salts, chiefly sodium bromide, and was less soluble than the present product.

Trimethyltetradecylammonium bromide

Empirical formula: $C_{17}H_{38}BrN$

Molecular weight: 336.40

CAS number: [1119-97-7]

Synonyms: myristyltrimethylammonium bromide; tetradecyltrimethylammonium bromide; *N*,*N*,*N*-trimethyl-1-tetradecanaminium bromide.

Safety:

LD_{50} (mouse, IV): 12 mg/kg(9)
LD_{50} (rat, IV): 15 mg/kg

18 Comments

As a precaution against contamination with *Pseudomonas* species resistant to cetrimide, stock solutions may be further protected by adding at least 7% v/v ethanol or 4% v/v propan-2-ol.

The EINECS number for cetrimide is 214-291-9.

19 Specific References

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21 Authors

SC Owen.

22 Date of Revision

15 August 2005.

Cetyl Alcohol

1 Nonproprietary Names

BP: Cetyl alcohol
JP: Cetanol
PhEur: Alcohol cetylicus
USPNF: Cetyl alcohol

2 Synonyms

Avol; *Cachalot*; *Crodacol C70*; *Crodacol C90*; *Crodacol C95*; ethal; ethol; 1-hexadecanol; *n*-hexadecyl alcohol; *Hyfatol 16-95*; *Hyfatol 16-98*; *Kessco CA*; *Lanette 16*; *Lipocol C*; palmityl alcohol; *Rita CA*; *Tego Alkanol 16*.

3 Chemical Name and CAS Registry Number

Hexadecan-1-ol [36653-82-4]

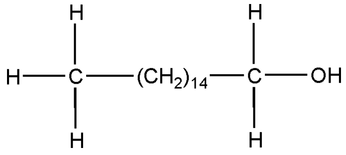
4 Empirical Formula and Molecular Weight

$C_{16}H_{34}O$ 242.44 (for pure material)

Cetyl alcohol, used in pharmaceutical preparations, is a mixture of solid aliphatic alcohols comprising mainly 1-hexadecanol ($C_{16}H_{34}O$). The USPNF 23 specifies not less than 90.0% of cetyl alcohol, the remainder consisting chiefly of related alcohols.

Commercially, many grades of cetyl alcohol are available as mixtures of cetyl alcohol (60–70%) and stearyl alcohol (20–30%), the remainder being related alcohols.

5 Structural Formula



$$H{-}\overset{H}{\underset{H}{C}}{-}(CH_2)_{14}{-}\overset{H}{\underset{H}{C}}{-}OH$$

6 Functional Category

Coating agent; emulsifying agent; stiffening agent.

7 Applications in Pharmaceutical Formulation or Technology

Cetyl alcohol is widely used in cosmetics and pharmaceutical formulations such as suppositories, modified-release solid dosage forms, emulsions, lotions, creams, and ointments.

In suppositories cetyl alcohol is used to raise the melting point of the base, and in modified-release dosage forms it may be used to form a permeable barrier coating. In lotions, creams, and ointments cetyl alcohol is used because of its emollient, water-absorptive, and emulsifying properties. It enhances stability, improves texture, and increases consistency. The emollient properties are due to absorption and retention of cetyl alcohol in the epidermis, where it lubricates and softens the skin while imparting a characteristic 'velvety' texture.

Cetyl alcohol is also used for its water absorption properties in water-in-oil emulsions. For example, a mixture of petrolatum and cetyl alcohol (19:1) will absorb 40–50% of its weight of water. Cetyl alcohol acts as a weak emulsifier of the water-in-oil type, thus allowing a reduction of the quantity of other emulsifying agents used in a formulation. Cetyl alcohol has also been reported to increase the consistency of water-in-oil emulsions.

In oil-in-water emulsions, cetyl alcohol is reported to improve stability by combining with the water-soluble emulsifying agent. The combined mixed emulsifier produces a close packed, monomolecular barrier at the oil–water interface which forms a mechanical barrier against droplet coalescence.

In semisolid emulsions, excess cetyl alcohol combines with the aqueous emulsifier solution to form a viscoelastic continuous phase that imparts semisolid properties to the emulsion and also prevents droplet coalescence. Therefore, cetyl alcohol is sometimes referred to as a 'consistency improver' or a 'bodying agent', although it may be necessary to mix cetyl alcohol with a hydrophilic emulsifier to impart this property.

It should be noted that pure or pharmacopeial grades of cetyl alcohol may not form stable semisolid emulsions and may not show the same physical properties as grades of cetyl alcohol that contain significant amounts of other similar alcohols. *See* Section 4.

See Table I.

Table I: Uses of cetyl alcohol.

Use	Concentration (%)
Emollient	2–5
Emulsifying agent	2–5
Stiffening agent	2–10
Water absorption	5

8 Description

Cetyl alcohol occurs as waxy, white flakes, granules, cubes, or castings. It has a faint characteristic odor and bland taste.

9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Boiling point:
316–344°C;
344°C for pure material.
Density: 0.908 g/cm^3
Flash point: 165°C
Melting point:
45–52°C;
49°C for pure material.
Refractive index: n_D^{79} = 1.4283 for pure material.
Solubility: freely soluble in ethanol (95%) and ether, solubility increasing with increasing temperature; practically insoluble

Table II: Pharmacopeial specifications for cetyl alcohol.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	—	+	+
Characters	—	+	—
Melting range	47–53°C	46–52°C	—
Residue on ignition	⩽0.05%	—	—
Ester value	⩽2.0	—	—
Alkali	+	—	—
Acid value	⩽1.0	⩽1.0	⩽2
Iodine value	⩽2.0	⩽2.0	⩽5
Hydroxyl value	210–232	218–238	
218–238			
Saponification value	—	⩽2.0	—
Clarity and color of solution	+	+	—
Assay	—	—	⩾90.0%

in water. Miscible when melted with fats, liquid and solid paraffins, and isopropyl myristate.

Specific gravity: ≈ 0.81 g/cm^3 at 50°C

Viscosity (dynamic): ≈ 7 mPa s (7 cP) at 50°C

11 Stability and Storage Conditions

Cetyl alcohol is stable in the presence of acids, alkalis, light, and air; it does not become rancid. It should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatible with strong oxidizing agents. Cetyl alcohol is responsible for lowering the melting point of ibuprofen, which results in sticking tendencies during the process of film coating ibuprofen crystals.(1)

13 Method of Manufacture

Cetyl alcohol may be manufactured by a number of methods such as esterification and hydrogenolysis of fatty acids or by catalytic hydrogenation of the triglycerides obtained from coconut oil or tallow. Cetyl alcohol may be purified by crystallization and distillation.

14 Safety

Cetyl alcohol is mainly used in topical formulations, although it has also been used in oral and rectal preparations.

Cetyl alcohol has been associated with allergic delayed-type hypersensitivity reactions in patients with stasis dermatitis.(2) Cross-sensitization with cetostearyl alcohol, lanolin, and stearyl alcohol has also been reported.(3,4) It has been suggested that hypersensitivity may be caused by impurities in commercial grades of cetyl alcohol since highly refined cetyl alcohol (99.5%) has not been associated with hypersensitivity reactions.(5)

LD_{50} (mouse, IP): 1.6 g/kg(6)
LD_{50} (mouse, oral): 3.2 g/kg
LD_{50} (rat, IP): 1.6 g/kg
LD_{50} (rat, oral): 5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (ophthalmic preparations, oral capsules and tablets, otic and rectal preparations, topical aerosols, creams, emulsions, ointments and solutions, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Cetostearyl alcohol; stearyl alcohol.

18 Comments

The EINECS number for cetyl alcohol is 253-149-0.

19 Specific References

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21 Authors

HM Unvala.

22 Date of Revision

12 April 2005.

Cetylpyridinium Chloride

1 Nonproprietary Names

BP: Cetylpyridinium chloride
PhEur: Cetylpridinii chloridum
USP: Cetylpyridinium chloride

2 Synonyms

C16-alkylpyridinium chloride; *Cepacol*; *Cepacol chloride*; *Cetamiun*; cetyl pyridium chloride; *Dobendan*; hexadecylpyridinium chloride; 1-hexadecylpyridinium chloride; *Medilave*; *Pristacin*; *Pyrisept*.

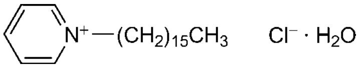
3 Chemical Name and CAS Registry Number

1-Hexadecylpyridinium chloride [123-03-5]
1-Hexadecylpyridinium chloride monohydrate [6004-24-6]

4 Empirical Formula and Molecular Weight

$C_{21}H_{38}ClN$	339.9 (for anhydrous)
$C_{21}H_{38}ClN{\cdot}H_2O$	358.1 (for monohydrate)

5 Structural Formula



6 Functional Category

Antimicrobial preservative; antiseptic; cationic surfactant; disinfectant; solubilizing agent; wetting agent.

7 Applications in Pharmaceutical Formulation or Technology

Cetylpyridinium chloride is a quaternary ammonium cationic surfactant, used in pharmaceutical and cosmetic formulations as an antimicrobial preservative; *see* Section 10. It is used therapeutically as an antiseptic agent; used alone or in combination with other drugs for oral and throat care; used in nonparenteral formulations licensed in the UK; and used in oral and inhalation preparations at concentrations of 0.02–1.5 mg (*see* Section 16).

Mouthwashes containing cetylpyridinium chloride have been shown to inhibit plaque formation,(1–3) although efficacy is variable owing to limited published data.(4,5)

8 Description

Cetylypyridinium chloride is a white powder with a characteristic odor. It is slightly soapy to the touch.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for cetylpyridinium chloride.

Test	PhEur 2005	USP 28
Absorbance	+	+
Acidity	+	+
Amines and amine salts	+	—
Appearance of solution	+	—
Characters	+	—
Heavy metals	—	⩽0.002%
Identification	+	+
Melting range	—	80.0–84.0°C
Organic volatile impurities	—	+
Pyridine	—	+
Residue on ignition	⩽0.2%	⩽0.2%
Water	4.5–5.5%	4.5–5.5%
Assay	96.0–101.0%	99.0–102.0%

10 Typical Properties

Antibacterial activity: bactericidal to Gram-positive bacteria; relatively ineffective against some Gram-negative bacteria.(6) Cetylpyridinium chloride is also antibacterial against a number of oral bacteria;(7) *see* Table II.(8)

Melting point: 80–83°C

Solubility: freely soluble in water; very soluble in chloroform; very slightly soluble in ether; insoluble in acetone, acetic acid, and ethanol.

Table II: Minimum inhibitory concentrations (MICs) for cetylpyridinium chloride.(8)

Microorganism	MIC (μg/mL)
Staphylococcus aureus	<2.0
Bacillus subtilis	<2.0
Salmonella typhimurium	8.0
Pseudomonas aeruginosa	16.0
Streptococcus pyogenes	<2.0

Critical micelle concentration: 0.34 g/L (water, 25°C).(9,10)

11 Stability and Storage Conditions

Cetylpyridinium chloride is stable under normal conditions. It should be stored in well-closed containers.

12 Incompatibilities

Incompatible with strong oxidizing agents and bases. It is also incompatible with methylcellulose.

Magnesium stearate suspensions in cetylpyridinium chloride have been shown to significantly reduce its antimicrobial activity. This is due to the absorption of cetylpyridinium chloride on magnesium stearate.(11) The cetylpyridinium chloride ion also interacts with gelatin, resulting in reduced bioavailability.(12)

13 Method of Manufacture

Cetylpyridinium chloride is prepared from cetyl chloride by treatment with pyridine.

14 Safety

Cetylpyridinium chloride is used widely in mouthwashes as a bactericidal antiseptic. It is generally regarded as a relatively nontoxic material when used at a concentration of 0.05% w/v, although minor side effects such as mild burning sensations on the tongue have been reported.(13)

At higher concentrations, cetylpyridinium chloride may damage the mucous membranes in the mouth. It is harmful when ingested or inhaled. It can cause eye irritation, and is irritant to the respiratory system and the skin.

LD_{50} (rat, IP): 0.006 g/kg(14)
LD_{50} (rat, IV): 0.03 g/kg
LD_{50} (rat, oral): 0.2 g/kg
LD_{50} (rat, SC): 0.25 g/kg
LD_{50} (mouse, IP): 0.01 g/kg
LD_{50} (mouse, oral): 0.108 g/kg
LD_{50} (rabbit, oral): 0.4 g/kg
LD_{50} (rabbit, IV): 0.036 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled. When significant quantities are being handled, the use of a respirator with an appropriate gas filter is advised. When heated to decomposition, cetylpyridinium chloride emits very toxic fumes of NO_x and Cl^-. Eye protection, gloves and adequate ventilation are recommended.

16 Regulatory Status

Included in nonparenteral formulations licensed in the UK. Included in the FDA Inactive Ingredients Guide, for use in inhalation and oral preparations. Reported in the EPA TSCA Inventory. It is not approved for use in Japan. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Cetylpyridinium bromide.

Cetylpyridinium bromide

Empirical formula: $C_{21}H_{38}BrN$
Molecular weight: 384.45
CAS number: [140-72-7]
Synonyms: *Aceloquat CPB*; *Bromocet*; *Cetapharm*; *Cetasol*; *N*-cetylpyridinium bromide; hexadexylpyridinium bromide; *Nitrogenol*; *Seprison*; *Sterogenol.*

18 Comments

Cetylpyridinium chloride has also been studied for use as an antimicrobial preservative for meat(15) and vegetables.(16) However, the residual levels after treatment are considered excessive for human consumption; *see* Section 14.

The EINECS number for cetylpyridinium chloride is 204-593-9.

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21 Authors

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22 Date of Revision

1 September 2005.

Chitosan

1 Nonproprietary Names

BP: Chitosan hydrochloride
PhEur: Chitosani hydrochloridum

2 Synonyms

2-Amino-2-deoxy-(1,4)-β-D-glucopyranan; deacetylated chitin; deacetylchitin; β-1,4-poly-D-glucosamine; poly-D-glucosamine; poly-(1,4-β-D-glucopyranosamine).

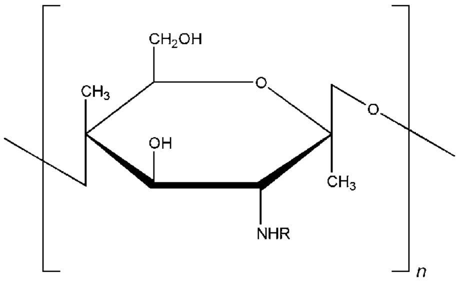
3 Chemical Name and CAS Registry Number

Poly-β-(1,4)-2-Amino-2-deoxy-D-glucose [9012-76-4]

4 Empirical Formula and Molecular Weight

Partial deacetylation of chitin results in the production of chitosan, which is a polysaccharide comprising copolymers of glucosamine and *N*-acetylglucosamine. Chitosan is the term applied to deacetylated chitins in various stages of deacetylation and depolymerization and it is therefore not easily defined in terms of its exact chemical composition. A clear nomenclature with respect to the different degrees of *N*-deacetylation between chitin and chitosan has not been defined,(1–3) and as such chitosan is not one chemical entity but varies in composition depending on the manufacturer. In essence, chitosan is chitin sufficiently deacetylated to form soluble amine salts. The degree of deacetylation necessary to obtain a soluble product must be greater than 80–85%. Chitosan is commercially available in several types and grades that vary in molecular weight by 10 000–1 000 000, and vary in degree of deacetylation and viscosity.(4)

5 Structural Formula



R = H or $COCH_3$

6 Functional Category

Coating agent; disintegrant; film-forming agent; mucoadhesive; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Chitosan is used in cosmetics and is under investigation for use in a number of pharmaceutical formulations. The suitability and performance of chitosan as a component of pharmaceutical formulations for drug delivery applications has been investigated in numerous studies.(3,5–8) These include controlled drug delivery applications,(9–14) use as a component of mucoadhesive dosage forms,(15,16) rapid release dosage forms,(17,18) improved peptide delivery,(19,20) colonic drug delivery systems,(21,22) and use for gene delivery.(23) Chitosan has been processed into several pharmaceutical forms including gels,(24,25) films,(11,12,26,27) beads,(28,29) microspheres,(30,31) tablets,(32,33) and coatings for liposomes.(34) Furthermore, chitosan may be processed into drug delivery systems using several techniques including spray-drying,(15,16) coacervation,(35) direct compression,(32) and conventional granulation processes.(36)

8 Description

Chitosan occurs as odorless, white or creamy-white powder or flakes. Fiber formation is quite common during precipitation and the chitosan may look 'cottonlike'.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for chitosan.

Test	PhEur 2005
Identification	+
Characters	+
Appearance of solution	+
Matter insoluble in water	≤0.5%
pH (1% w/v solution)	4.0–6.0
Viscosity	+
Degree of deacetylation	+
Chlorides	10.0–20.0%
Heavy metals	≤40 ppm
Loss on drying	≤10%
Sulfated ash	≤1.0%

10 Typical Properties

Chitosan is a cationic polyamine with a high charge density at pH <6.5; and so adheres to negatively charged surfaces and chelates metal ions. It is a linear polyelectrolyte with reactive hydroxyl and amino groups (available for chemical reaction and salt formation).(7) The properties of chitosan relate to its polyelectrolyte and polymeric carbohydrate character. The presence of a number of amino groups allows chitosan to react chemically with anionic systems, which results in alteration of physicochemical characteristics of such combinations. The nitrogen in chitosan is mostly in the form of primary aliphatic amino groups. Chitosan therefore undergoes reactions typical of amines: for example, *N*-acylation and Schiff reactions.(3) Almost all functional properties of chitosan depend on the chain length, charge density, and charge distribution.(8) Numerous studies have demonstrated that the salt form, molecular weight, and degree of deacetylation as well as pH at which the chitosan is used all influence how this polymer is utilized in pharmaceutical applications.(7)

Acidity/alkalinity: pH = 4.0–6.0 (1% w/v aqueous solution)

Density: 1.35–1.40 g/cm^3

Glass transition temperature: 203°C(37)

Moisture content: chitosan adsorbs moisture from the atmosphere, the amount of water adsorbed depending upon the initial moisture content and the temperature and relative humidity of the surrounding air.(38)

Particle size distribution: <30 μm

Solubility: sparingly soluble in water; practically insoluble in ethanol (95%), other organic solvents, and neutral or alkali solutions at pH above approximately 6.5. Chitosan dissolves readily in dilute and concentrated solutions of most organic acids and to some extent in mineral inorganic acids (except phosphoric and sulfuric acids). Upon dissolution, amine groups of the polymer become protonated, resulting in a positively charged polysaccharide (RNH_3^+) and chitosan salts (chloride, glutamate, etc.) that are soluble in water; the solubility is affected by the degree of deacetylation.(7) Solubility is also greatly influenced by the addition of salt to the solution. The higher the ionic strength, the lower the solubility as a result of a salting-out effect, which leads to the precipitation of chitosan in solution.(39) When chitosan is in solution, the repulsions between the deacetylated units and their neighboring glucosamine units cause it to exist in an extended conformation. Addition of an electrolyte reduces this effect and the molecule possesses a more random, coil-like conformation.(40)

Viscosity (dynamic): a wide range of viscosity types is commercially available. Owing to its high molecular weight and linear, unbranched structure, chitosan is an excellent viscosity-enhancing agent in an acidic environment. It acts as a pseudo-plastic material, exhibiting a decrease in viscosity with increasing rates of shear.(7) The viscosity of chitosan solutions increases with increasing chitosan concentration, decreasing temperature, and increasing degree of deacetylation; *see* Table II.(40)

Table II: Typical viscosity (dynamic) values for chitosan 1% w/v solutions in different acids.(40)

Acid	1% acid concentration		5% acid concentration		10% acid concentration	
	Viscosity (mPa s)	pH	Viscosity (mPa s)	pH	Viscosity (mPa s)	pH
Acetic	260	4.1	260	3.3	260	2.9
Adipic	190	4.1	—	—	—	—
Citric	35	3.0	195	2.3	215	2.0
Formic	240	2.6	185	2.0	185	1.7
Lactic	235	3.3	235	2.7	270	2.1
Malic	180	3.3	205	2.3	220	2.1
Malonic	195	2.5	—	—	—	—
Oxalic	12	1.8	100	1.1	100	0.8
Tartaric	52	2.8	135	2.0	160	1.7

11 Stability and Storage Conditions

Chitosan powder is a stable material at room temperature, although it is hygroscopic after drying. Chitosan should be stored in a tightly closed container in a cool, dry place. The PhEur 2005 specifies that chitosan should be stored at a temperature of 2–8°C.

12 Incompatibilities

Chitosan is incompatible with strong oxidizing agents.

13 Method of Manufacture

Chitosan is manufactured commercially by chemically treating the shells of crustaceans such as shrimps and crabs. The basic manufacturing process involves the removal of proteins by treatment with alkali and of minerals such as calcium carbonate and calcium phosphate by treatment with acid.(3,40) Before these treatments, the shells are ground to make them more accessible. The shells are initially deproteinized by treatment with an aqueous sodium hydroxide 3–5% solution. The resulting product is neutralized and calcium is removed by treatment with an aqueous hydrochloric acid 3–5% solution at room temperature to precipitate chitin. The chitin is dried so that it can be stored as a stable intermediate for deacetylation to chitosan at a later stage. *N*-deacetylation of chitin is achieved by treatment with an aqueous sodium hydroxide 40–45% solution at elevated temperature (110°C), and the precipitate is washed with water. The crude sample is dissolved in acetic acid 2% and the insoluble material is removed. The resulting clear supernatant solution is neutralized with aqueous sodium hydroxide solution to give a purified white precipitate of chitosan. The product can then be further purified and ground to a fine uniform powder or granules.(1) The animals from which chitosan is derived must fulfil the requirements for the health of animals suitable for human consumption to the satisfaction of the competent authority. The method of production must consider inactivation or removal of any contamination by viruses or other infectious agents.

14 Safety

Chitosan is being investigated widely for use as an excipient in oral and other pharmaceutical formulations. It is also used in cosmetics. Chitosan is generally regarded as a nontoxic and nonirritant material. It is biocompatible(41) with both healthy and infected skin.(42) Chitosan has been shown to be biodegradable.(3,41)

LD_{50} (mouse, oral): >16 g/kg(43)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Chitosan is combustible; open flames should be avoided. Chitosan is temperature-sensitive and should not be heated above 200°C. Airborne chitosan dust may explode in the presence of a source of ignition, depending on its moisture content and particle size. Water, dry chemicals, carbon dioxide, sand, or foam fire-fighting media should be used.

Chitosan may cause skin or eye irritation. It may be harmful if absorbed through the skin or if inhaled and may be irritating to mucous membranes and the upper respiratory tract. Eye and skin protection and protective clothing are recommended; wash thoroughly after handling. Prolonged or repeated exposure (inhalation) should be avoided by handling in a well-ventilated area and wearing a respirator.

16 Regulatory Status

Chitosan is registered as a food supplement in some countries.

17 Related Substances

See Section 18.

18 Comments

Chitosan derivatives are easily obtained under mild conditions and can be considered as substituted glucens.(3)

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21 Authors

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22 Date of Revision

28 August 2005.

Chlorhexidine

1 Nonproprietary Names

BP:	Chlorhexidine acetate Chlorhexidine gluconate solution Chlorhexidine hydrochloride
JP:	Chlorhexidine gluconate solution Chlorhexidine hydrochloride
PhEur:	Chlorhexidini diacetas Chlorhexidini digluconatis solutio Chlorhexidini dihydrochloridum Chlorhexidine gluconate solution

Chlorhexidine is usually encountered as the acetate, gluconate, or hydrochloride salt, and a number of pharmacopeias contain monographs for such materials. *See* Sections 9 and 17.

2 Synonyms

1,6-bis[*N*′-(*p*-Chlorophenyl)-*N*^{5}-biguanido]hexane; *N*,*N*″-bis (4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecane-diimidamide; 1,6-di(4′-chlorophenyldiguanido)hexane.

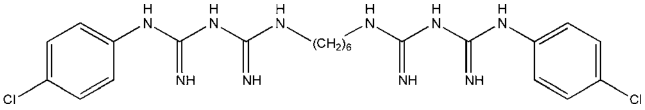
3 Chemical Name and CAS Registry Number

N,*N*″-Bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecanediimidamide [55-56-1]

4 Empirical Formula and Molecular Weight

$C_{22}H_{30}Cl_2N_{10}$ 505.48

5 Structural Formula



6 Functional Category

Antimicrobial preservative; antiseptic.

7 Applications in Pharmaceutical Formulation or Technology

Chlorhexidine salts are widely used in pharmaceutical formulations in Europe and Japan for their antimicrobial properties.(1,2) Although mainly used as disinfectants, chlorhexidine salts are also used as antimicrobial preservatives.

As excipients, chlorhexidine salts are mainly used for the preservation of eye-drops at a concentration of 0.01% w/v; generally the acetate or gluconate salt is used for this purpose. Solutions containing 0.002–0.006% w/v chlorhexidine gluconate have also been used for the disinfection of hydrophilic contact lenses.

For skin disinfection, chlorhexidine has been formulated as a 0.5% w/v solution in 70% v/v ethanol and, in conjunction with detergents, as a 4% w/v surgical scrub. Chlorhexidine salts may also be used in topical antiseptic creams, mouthwashes, dental gels, and in urology for catheter sterilization and bladder irrigation.(1–4)

Chlorhexidine salts have additionally been used as constituents of medicated dressings, dusting powders, sprays, and creams.

8 Description

Chlorhexidine occurs as an odorless, bitter tasting, white crystalline powder. *See* Section 17 for information on chlorhexidine salts.

9 Pharmacopeial Specifications

See Table I.

See also Section 17.

10 Typical Properties

Antimicrobial activity: chlorhexidine and its salts exhibit antimicrobial activity against Gram-positive and Gram-negative microorganisms.(5) At the low concentrations normally used for preservation and antisepsis, chlorhexidine salts are rapidly bactericidal. However, species of *Proteus* and *Pseudomonas* are less susceptible to chlorhexidine, which is also inactive against acid-fast bacilli, bacterial spores, and some fungi. Chlorhexidine salts are effective against some lipophilic viruses such as adenovirus, herpes virus, and influenza virus. Optimum antimicrobial activity occurs at pH 5–7. Above pH 8, the chlorhexidine base may precipitate from aqueous solutions.

Bacteria (Gram-positive): chlorhexidine salts are active against most species; the minimum inhibitory concentration (MIC) is normally in the range 1–10 μg/mL, although much higher concentrations are necessary for *Streptococcus faecalis*. Typical MIC values are shown in Table II.

Bacteria (Gram-negative): chlorhexidine salts are less active against Gram-negative species than against Gram-positive species. Typical MICs are 1–15 μg/mL, but pseudomonads, particularly *Pseudomonas aeruginosa*, may be more resistant. *Serratia marcescens* may also be resistant. Combinations of chlorhexidine acetate with the following substances have shown enhanced or more than additive activity towards *Pseudomonas aeruginosa*: benzalkonium chloride; benzyl alcohol; bronopol; edetic acid; phenylethanol, and phenylpropanol.(6,7) Typical MIC values are shown in Table III.

Table I: Pharmacopeial specifications for chlorhexidine.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
pH			
Chlorhexidine gluconate solution	5.5–7.0	5.5–7.0	5.5–7.0
Relative density			
Chlorhexidine gluconate solution	1.06–1.07	1.06–1.07	1.06–1.07
4-Chloroaniline			
Chlorhexidine acetate	—	≤0.25%	—
Chlorhexidine gluconate solution	+	+	≤500 µg/mL
Chlorhexidine hydrochloride	+	≤500 ppm	—
Related substances	—	+	+
Loss on drying			
Chlorhexidine acetate	—	≤3.5%	—
Chlorhexidine hydrochloride	≤2.0%	≤1.0%	—
Sulfated ash			
Chlorhexidine acetate	—	≤0.15%	—
Chlorhexidine gluconate solution	≤0.10%	—	—
Chlorhexidine hydrochloride	≤0.10%	≤0.1%	—
Heavy metals	≤10 ppm	—	—
Arsenic			
Chlorhexidine acetate	≤2 ppm	—	—
Chlorhexidine hydrochloride	≤2 ppm	—	—
Assay			
Chlorhexidine acetate	—	98.0–101.0%	—
Chlorhexidine gluconate solution	19.0–21.0%	19.0–21.0%	19.0–21.0%
Chlorhexidine hydrochloride	≥98.0%	98.0–101.0%	—

Table II: Typical minimum inhibitory concentrations (MIC) of chlorhexidine against Gram-positive bacteria.

Microorganism	MIC (µg/mL)
Bacillus spp.	1.0–3.0
Clostridium spp.	1.8–70.0
Corynebacterium spp.	5.0–10.0
Staphylococcus spp.	0.5–6.0
Streptococcus faecalis	2000–5000
Streptococcus spp.	0.1–7.0

Fungi: chlorhexidine salts are slowly active against molds and yeasts, although they are generally less potent in their inhibitory activity against fungi than against bacteria. Typical MIC values are shown in Table IV.

Table III: Typical MIC values of chlorhexidine against Gram-negative bacteria.

Microorganism	MIC (µg/mL)
Escherichia coli	2.5–7.5
Klebsiella spp.	1.5–12.5
Proteus spp.	3–100
Pseudomonas spp.	3–60
Serratia marcescens	3–75
Salmonella spp.	1.6–15

Table IV: Typical MIC values of chlorhexidine against fungi.

Microorganism	MIC (µg/mL)
Aspergillus spp.	75.0–500.0
Candida albicans	7.0–15.0
Microsporum spp.	12.0–18.0
Penicillium spp.	150.0–200.0
Saccharomyces spp.	50.0–125.0
Trichophyton spp.	2.5–14.0

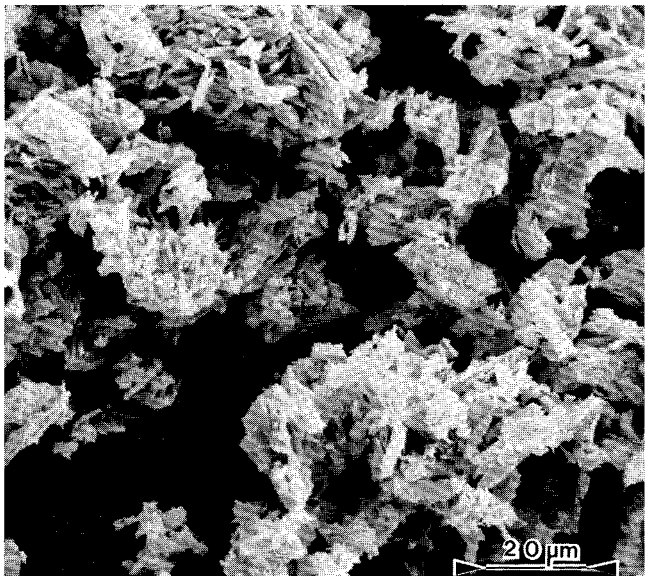
Spores: chlorhexidine salts are inactive against spores at normal room temperature.(8) At 98–100°C there is some activity against mesophilic spores.

Critical micelle concentration: ≈0.6% w/v (depends on other ions in solution).(9)

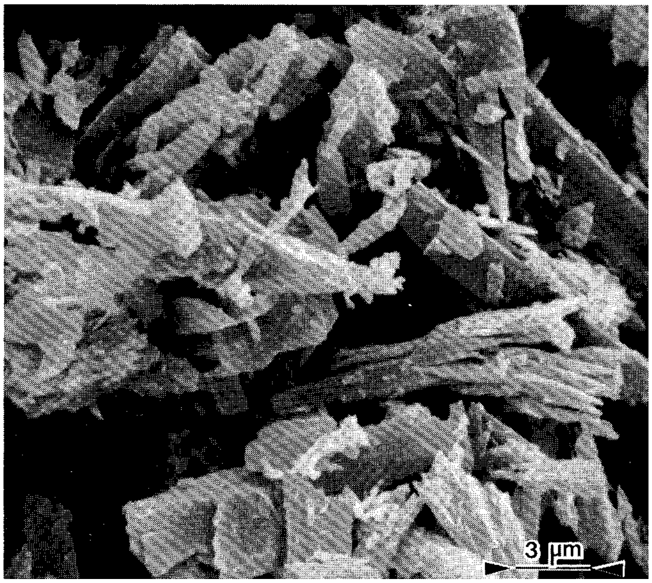
Melting point: 132–134°C

See also Section 17 for additional information.

SEM: 1
Excipient: Chlorhexidine
Manufacturer: SST Corp.
Magnification: 600×



SEM: 2
Excipient: Chlorhexidine
Manufacturer: SST Corp.
Magnification: 2400×



11 Stability and Storage Conditions

Chlorhexidine and its salts are stable at normal storage temperatures when in the powdered form. However, chlorhexidine hydrochloride is hygroscopic, absorbing significant amounts of moisture at temperatures up to 37°C and relative humidities up to 80%.

Heating to 150°C causes decomposition of chlorhexidine and its salts, yielding trace amounts of 4-chloroaniline. However, chlorhexidine hydrochloride is more thermostable than the acetate and can be heated at 115°C for 1 hour without appreciable formation of 4-chloroaniline.

In aqueous solution, chlorhexidine salts may undergo hydrolysis to form 4-chloroaniline. Following autoclaving of a 0.02% w/v chlorhexidine gluconate solution at pH 9 for 30 minutes at 120°C, it was found that 1.56% w/w of the original chlorhexidine content had been converted into 4-chloroaniline; for solutions at pH 6.3 and 4.7 the 4-chloroaniline content was 0.27% w/w and 0.13% w/w, respectively, of the original gluconate content.(10) In buffered 0.05% w/v chlorhexidine acetate solutions, maximum stability occurs at pH 5.6.

When chlorhexidine solutions were autoclaved at various time and temperature combinations, the rate of hydrolysis increased markedly above 100°C, and as pH increased or decreased from pH 5.6. At a given pH, chlorhexidine gluconate produced more 4-chloroaniline than the acetate.

It was predicted that in an autoclaved solution containing 0.01% w/v chlorhexidine, the amount of 4-chloroaniline formed would be about 0.00003%. At these low concentrations there would be little likelihood of any toxic hazard as a result of the increase in 4-chloroaniline content in the autoclaved solution.

Chlorhexidine solutions and aqueous-based products may be packaged in glass and high-density polyethylene or polypropylene bottles provided that they are protected from light. If not protected from light, chlorhexidine solutions containing 4-chloroaniline discolor owing to polymerization of the 4-chloroaniline.(11–13)

Cork-based closures or liners should not be used in packaging in contact with chlorhexidine solutions.

As a precaution against contamination with *Pseudomonas* species resistant to chlorhexidine, stock solutions may be protected by the inclusion of 7% w/v ethanol or 4% w/v propan-2-ol.

Chlorhexidine salts, and their solutions, should be stored in well-closed containers, protected from light, in a cool, dry place.

12 Incompatibilities

Chlorhexidine salts are cationic in solution and are therefore incompatible with soaps and other anionic materials. Chlorhexidine salts are compatible with most cationic and nonionic surfactants, but in high concentrations of surfactant chlorhexidine activity can be substantially reduced owing to micellar binding.

Chlorhexidine salts of low aqueous solubility are formed and may precipitate from chlorhexidine solutions of concentration greater than 0.05% w/v, when in the presence of inorganic acids, certain organic acids, and salts (e.g. benzoates, bicarbonates, borates, carbonates, chlorides, citrates, iodides, nitrates, phosphates, and sulfates).(14) At chlorhexidine concentrations below 0.01% w/v precipitation is less likely to occur.

In hard water, insoluble salts may form owing to interaction with calcium and magnesium cations. Solubility may be enhanced by the inclusion of surfactants such as cetrimide.

Other substances incompatible with chlorhexidine salts include viscous materials such as acacia, sodium alginate, sodium carboxymethylcellulose, starch, and tragacanth.(15,16) Also incompatible are brilliant green, chloramphenicol, copper sulfate, fluorescein sodium, formaldehyde, silver nitrate, and zinc sulfate.

Interaction has been reported between chlorhexidine gluconate and the hydrogel poly(2-hydroxyethyl methacrylate), which is a component of some hydrophilic contact lenses.(17,18)

13 Method of Manufacture

Chlorhexidine may be prepared either by condensation of polymethylene bisdicyandiamide with 4-chloroaniline hydrochloride or by condensation of 4-chlorophenyl dicyandiamine with hexamethylenediamine dihydrochloride. Chlorhexidine may also be synthesized from a series of biguanides.(19)

14 Safety

Chlorhexidine and its salts are widely used, primarily as topical disinfectants. As excipients, chlorhexidine salts are mainly used as antimicrobial preservatives in ophthalmic formulations.

Animal studies suggest that the acute oral toxicity of chlorhexidine is low, with little or no absorption from the gastrointestinal tract. However, although humans have consumed up to 2 g of chlorhexidine daily for 1 week, without untoward symptoms, chlorhexidine is not generally used as an excipient in orally ingested formulations.

Reports have suggested that there may be some systemic effects in humans following oral consumption of chlorhexidine.(20–22) Similarly, the topical application of chlorhexidine or its salts produced evidence of very slight percutaneous absorption of chlorhexidine, although the concentrations absorbed were insufficient to produce systemic adverse effects.(23)

Severe hypersensitivity reactions, including anaphylactic shock, have been reported following the topical administration of chlorhexidine,(24–28) although such instances are rare given the extensive use of chlorhexidine and it salts.

In ophthalmic preparations, irritation of the conjunctiva occurs with chlorhexidine solutions of concentration stronger than 0.1% w/v. Accidental eye contact with 4% w/v chlorhexidine gluconate solution may result in corneal damage.(29)

The aqueous concentration of chlorhexidine normally recommended for contact with mucous surfaces is 0.05% w/v. At this concentration, there is no irritant effect on soft tissues, nor is healing delayed. The gluconate salt (1% w/v) is frequently used in creams, lotions, and disinfectant solutions.

Direct instillation of chlorhexidine into the middle ear can result in ototoxicity;(30) when used in dental preparations, staining of teeth and oral lesions may occur.(31,32)

Use of chlorhexidine on the brain or meninges is extremely dangerous.

LD_{50} (mouse, IP): 0.04 g/kg(33)
LD_{50} (mouse, oral): 2.52 g/kg
LD_{50} (rat, IP): 0.06 g/kg
LD_{50} (rat, IV): 0.02 g/kg
LD_{50} (rat, oral): 9.2 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. The dust of chlorhexidine and its salts may be irritant to the skin, eyes, and respiratory tract. Gloves, eye protection, and a respirator are recommended.

16 Regulatory Status

Chlorhexidine salts are included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Chlorhexidine acetate; chlorhexidine gluconate; chlorhexidine hydrochloride.

Chlorhexidine acetate

Empirical formula: $C_{22}H_{30}Cl_2N_{10}\cdot 2C_2H_4O_2$
Molecular weight: 625.64
CAS number: [56-95-1]
Synonyms: chlorhexidini acetas; chlorhexidine diacetate; 1,1′-hexamethylenebis[5-(4-chlorophenyl)biguanide] diacetate; *Hibitane diacetate*.
Appearance: a white or almost white, microcrystalline powder.
Melting point: 154°C
Moisture content: chlorhexidine acetate is hygroscopic, absorbing significant amounts of moisture at relative humidities up to about 80% and temperatures up to 37°C.
Partition coefficients:
Mineral oil : water = 0.075;
Peanut oil : water = 0.04.
Solubility: soluble 1 in 15 of ethanol (95%), 1 in 55 of water; slightly soluble in glycerin and propylene glycol.
Safety:
LD_{50} (mouse, IP): 0.04 g/kg(33)
LD_{50} (mouse, IV): 0.03 g/kg
LD_{50} (mouse, oral): 2 g/kg
LD_{50} (mouse, SC): 0.33 g/kg
Comments: aqueous solutions may be sterilized by autoclaving; the solutions should not be alkaline or contain other ingredients that affect the stability of chlorhexidine. *See* Sections 11 and 12.

The EINECS number for chlorhexidine acetate is 200-302-4.

Chlorhexidine gluconate

Empirical formula: $C_{22}H_{30}Cl_2N_{10}\cdot 2C_6H_{12}O_7$
Molecular weight: 897.88
CAS number: [18472-51-0]
Synonyms: chlorhexidine digluconate; chlorhexidini digluconatis; 1,1′-hexamethylenebis[5-(4-chlorophenyl)biguanide] digluconate; *Hibiclens*; *Hibiscrub*; *Hibitane*; *Unisept*.
Appearance: chlorhexidine gluconate is usually used as an almost colorless or pale yellow-colored aqueous solution.
Acidity/alkalinity: pH = 5.5–7.0 for a 5% w/v aqueous dilution.
Solubility: miscible with water; soluble in acetone and ethanol (95%).
Safety:
LD_{50} (mouse, IV): 0.02 g/kg(33)
LD_{50} (mouse, oral): 1.8 g/kg
LD_{50} (mouse, SC): 1.14 g/kg
LD_{50} (rat, IV): 0.02 g/kg
LD_{50} (rat, oral): 2 g/kg
LD_{50} (rat, SC): 3.32 g/kg
Comments: the commercially available 5% w/v chlorhexidine gluconate solution contains a nonionic surfactant to prevent precipitation and is not suitable for use in body cavities or for the disinfection of surgical instruments containing cemented glass components. Aqueous dilutions of commercially available chlorhexidine gluconate solutions may be sterilized by autoclaving. *See* Sections 11 and 12.

The EINECS number for chlorhexidine gluconate is 242-354-0.

Chlorhexidine hydrochloride

Empirical formula: $C_{22}H_{30}Cl_2N_{10}\cdot 2HCl$
Molecular weight: 578.44
CAS number: [3697-42-5]
Synonyms: chlorhexidine dihydrochloride; chlorhexidini hydrochloridum; 1,1′-hexamethylenebis[5-(4-chlorophenyl)biguanide]dihydrochloride.
Appearance: a white or almost white, crystalline powder.
Melting point: 261°C, with decomposition.
Solubility: sparingly soluble in water; very slightly soluble in ethanol (95%); soluble 1 in 50 of propylene glycol.
Safety: LD_{50} (mouse, SC): >5 g/kg(33)
Comments: chlorhexidine hydrochloride may be sterilized by dry heat. *See* Sections 11 and 12.

The EINECS number for chlorhexidine hydrochloride is 223-026-6.

18 Comments

The EINECS number for chlorhexidine is 200-238-7.

19 Specific References

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21 Authors

SC Owen.

22 Date of Revision

25 August 2005.

Chlorobutanol

1 Nonproprietary Names

BP: Chlorobutanol
JP: Chlorobutanol
PhEur: Chlorobutanolum anhydricum
USPNF: Chlorobutanol

2 Synonyms

Acetone chloroform; chlorbutanol; chlorbutol; trichloro-*tert*-butanol; β,β,β-trichloro-*tert*-butyl alcohol.

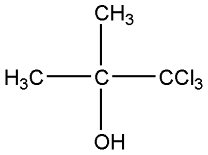
3 Chemical Name and CAS Registry Number

1,1,1-Trichloro-2-methyl-2-propanol [57-15-8]

4 Empirical Formula and Molecular Weight

$C_4H_7Cl_3O$ 177.46

5 Structural Formula



$$H_3C-\overset{\displaystyle CH_3 \atop |}{\underset{| \atop \displaystyle OH}{C}}-CCl_3$$

6 Functional Category

Antimicrobial preservative; plasticizer.

7 Applications in Pharmaceutical Formulation or Technology

Chlorobutanol is primarily used in ophthalmic or parenteral dosage forms as an antimicrobial preservative at concentrations up to 0.5% w/v; *see* Section 10. It is commonly used as an antibacterial agent for epinephrine solutions, posterior pituitary extract solutions, and ophthalmic preparations intended for the treatment of miosis. It is especially useful as an antibacterial agent in nonaqueous formulations. Chlorobutanol is also used as a preservative in cosmetics (*see* Section 16); as a plasticizer for cellulose esters and ethers; and has been used therapeutically as a mild sedative and local analgesic.

8 Description

Volatile, colorless or white crystals with a musty, camphoraceous odor.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for chlorobutanol.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	+	+	—
Melting point	⩾76°C	+	—
Anhydrous	—	≈95°C	—
Hemihydrate	—	≈78°C	—
Acidity	+	+	+
Water (anhydrous form)	⩽6.0%	⩽1.0%	⩽1.0%
Hemihydrate	—	4.5–5.5%	⩽6.0%
Chloride	⩽0.071%	+	⩽0.07%
Anhydrous	—	⩽300 ppm	—
Hemihydrate	—	⩽100 ppm	—
Residue on ignition	⩽0.10%	—	—
Sulfated ash	—	⩽0.1%	—
Organic volatile impurities	—	—	+
Assay (anhydrous basis)	⩾98.0%	98.0–101.0%	98.0–100.5%

Note: the JP 2001 and USPNF 23 allow either the anhydrous form or the hemihydrate; the PhEur 2005 includes them as separate monographs.

10 Typical Properties

Antimicrobial activity: chlorobutanol has both antibacterial and antifungal properties. It is effective against Gram-positive and Gram-negative bacteria and some fungi, e.g., *Candida albicans*, *Pseudomonas aeruginosa*, and *Staphylococcus albus*. Antimicrobial activity is bacteriostatic, rather than bactericidal, and is considerably reduced above pH 5.5. In addition, activity may also be reduced by increasing heat and by incompatibilities between chlorobutanol and other excipients or packaging materials; *see* Sections 11 and 12. However, activity may be increased by combination with other antimicrobial preservatives; *see* Section 18. Typical minimum inhibitory concentrations (MICs) are: Gram-positive bacteria 650 μg/mL; Gram-negative bacteria 1000 μg/mL; yeasts 2500 μg/mL; fungi 5000 μg/mL.

Boiling point: 167°C

Melting point:
76–78°C for the hemihydrate;
95–97°C for the anhydrous form.

Refractive index: $n_D^{25} = 1.4339$

Solubility: *see* Table II.

Table II: Solubility of chlorobutanol.

Solvent	Solubility at 20°C
Chloroform	Freely soluble
Ethanol (95%)	1 in 1
Ether	Freely soluble
Glycerin	1 in 10
Methanol	Freely soluble
Volatile oils	Freely soluble
Water	1 in 125

11 Stability and Storage Conditions

Chlorobutanol is volatile and readily sublimes. In aqueous solution degradation is catalyzed by hydroxide ions. Stability is good at pH 3 but becomes progressively worse with increasing pH.(1) The half-life at pH 7.5 for a chlorobutanol solution stored at 25°C was determined to be approximately 3 months.(2) In a 0.5% w/v aqueous chlorobutanol solution at room temperature, chlorobutanol is almost saturated and may crystallize out of solution if the temperature is reduced.

Losses of chlorobutanol also occur owing to its volatility, with appreciable amounts being lost during autoclaving; at pH 5 about 30% of chlorobutanol is lost.(3) Porous containers result in losses from solutions, and polyethylene containers result in rapid loss. Losses of chlorobutanol during autoclaving in polyethylene containers may be reduced by pre-autoclaving the containers in a solution of chlorobutanol; the containers should then be used immediately.(4) There is also appreciable loss of chlorobutanol through stoppers in parenteral vials.

The bulk material should be stored in a well-closed container at a temperature of 8–15°C.

12 Incompatibilities

Owing to problems associated with sorption, chlorobutanol is incompatible with plastic vials,(4–8) rubber stoppers, bentonite,(9) magnesium trisilicate,(9) polyethylene, and polyhydroxyethylmethacrylate, which has been used in soft contact lenses.(10) To a lesser extent, carboxymethylcellulose and polysorbate 80 reduce antimicrobial activity by sorption or complex formation.

13 Method of Manufacture

Chlorobutanol is prepared by condensing acetone and chloroform in the presence of solid potassium hydroxide.

14 Safety

Chlorobutanol is widely used as a preservative in a number of pharmaceutical formulations, particularly ophthalmic preparations. Although animal studies have suggested that chlorobutanol may be harmful to the eye, in practice the widespread use of chlorobutanol as a preservative in ophthalmic preparations has been associated with few reports of adverse reactions. A study of the irritation potential of a local anesthetic on the murine cornea indicated significant corneal surface damage in the presence of 0.5% w/v chlorobutanol, which may be related to the preservative's effective concentration.(11) Reported adverse reactions to chlorobutanol include: cardiovascular effects following intravenous administration of heparin sodium injection preserved with chlorobutanol;(12) neurological effects following administration of a large dose of morphine infusion preserved with chlorobutanol;(13) and hypersensitivity reactions, although these are regarded as rare.(14–16)

The lethal human dose of chlorobutanol is estimated to be 50–500 mg/kg.(17)

LD_{50} (dog, oral): 0.24 g/kg(18,19)
LD_{50} (mouse, oral): 0.99 g/kg
LD_{50} (rabbit, oral): 0.21 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Chlorobutanol may be irritant to the skin, eyes, and mucous membranes. Eye protection and gloves are recommended along with a respirator in poorly ventilated environments. There is a slight fire hazard on exposure to heat or flame.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IM, IV, and SC injections, inhalations, nasal, otic, ophthalmic, and topical preparations). Labeling must state 'contains chlorobutanol up to 0.5%'. Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

In the UK, the maximum concentration of chlorobutanol permitted for use in cosmetics, other than foams, is 0.5%. It is not suitable for use in aerosols.

17 Related Substances

Phenoxyethanol; phenylethyl alcohol.

18 Comments

It has been reported that a combination of chlorobutanol and phenylethanol, both at 0.5% w/v concentration, has shown greater antibacterial activity than either compound alone. An advantage of the use of this combination is that chlorobutanol dissolves in the alcohol; the resulting liquid can then be dissolved in an aqueous pharmaceutical preparation without the application of heat.

The EINECS number for chlorobutanol is 200-317-6.

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21 Authors

RA Nash.

22 Date of Revision

22 August 2005.

Chlorocresol

1 Nonproprietary Names

BP: Chlorocresol
PhEur: Chlorocresolum
USPNF: Chlorocresol

2 Synonyms

Aptal; *Baktol*; 4-chloro-*m*-cresol; *p*-chloro-*m*-cresol; 1-chloro-4-hydroxy-2-methylbenzene; 2-chloro-5-hydroxytoluene; 6-chloro-3-hydroxytoluene; 4-chloro-3-methylphenol; 3-methyl-4-chlorophenol; *Nipacide PC*; parachlorometacresol; PCMC.

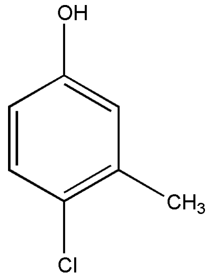
3 Chemical Name and CAS Registry Number

4-Chloro-3-methylphenol [59-50-7]

4 Empirical Formula and Molecular Weight

C_7H_7ClO 142.58

5 Structural Formula



6 Functional Category

Antimicrobial preservative; disinfectant.

7 Applications in Pharmaceutical Formulation or Technology

Chlorocresol is used as an antimicrobial preservative in cosmetics and pharmaceutical formulations. It is generally used in concentrations up to 0.2% in a variety of preparations except those intended for oral administration or that contact mucous membrane. Chlorocresol is effective against bacteria, spores, molds, and yeasts; it is most active in acidic media. Preservative efficacy may be reduced in the presence of some other excipients, particularly nonionic surfactants, *see* Sections 10 and 12.

In higher concentrations, chlorocresol is an effective disinfectant. *See* Table I.

Table I: Uses of chlorocresol.

Use	Concentration (%)
Eye drops	0.05
Injections	0.1
Shampoos and other cosmetics	0.1–0.2
Topical creams and emulsions	0.075–0.12

8 Description

Colorless or almost colorless, dimorphous crystals or crystalline powder with a characteristic phenolic odor.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for chlorocresol.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Appearance of solution	+	+
Melting range	64–67°C	63–66°C
Nonvolatile matter	⩽0.1%	⩽0.1%
Acidity or alkalinity	+	—
Related substances	+	—
Assay	98.0–101.0%	99.0–101.0%

10 Typical Properties

Antimicrobial activity: chlorocresol has bactericidal activity against both Gram-positive and Gram-negative organisms (including *Pseudomonas aeruginosa*), spores, molds, and yeasts. It is most active in acidic solutions, with antimicrobial effectiveness decreasing with increasing pH; it is inactive above pH 9. Antimicrobial activity may also be reduced by loss of chlorocresol from a formulation due to incompatibilities with packaging materials or other excipients, such as nonionic surfactants, *see* Section 12. Synergistic antimicrobial effects between chlorocresol and other antimicrobial preservatives, such as 2-phenylethanol, have been reported.(1,2) Reported minimum inhibitory concentrations (MICs) for chlorocresol are shown in Table III.(3) Like most antimicrobials, chlorocresol has a non-linear dose response.(4,5)

Bacteria: concentrations of approximately 0.08%, with a contact time of 10 minutes, are bactericidal. A typical MIC is 0.02%.

Fungi: chlorocresol is active against molds and yeasts. Fungicidal concentrations (after 24 hours of contact) are in the range 0.01–0.04%.

Table III: Minimum inhibitory concentrations (MICs) for chlorocresol.(3)

Microorganism	MIC (μg/mL)
Aspergillus niger	2500
Candida albicans	2500
Escherichia coli	1250
Klebsiella pneumoniae	625
Pseudomonas aeruginosa	1250
Pseudomonas fluorescens	1250
Staphylococcus aureus	625

Spores: at temperatures of 80°C or above and in concentrations greater than 0.012%, chlorocresol is active against spores. It is much less active at room temperature. Heating at 98–100°C for 30 minutes in the presence of 0.2% chlorocresol has previously been used as a compendial method for the sterilization of solutions of substances that would not withstand autoclaving.

Boiling point: 235°C

Dissociation constant: $pK_a = 9.2$

Flash point: 118°C

Melting point: dimorphous crystals with a melting point of 55.5°C and 65°C.

Partition coefficients: at 25°C
Liquid paraffin : water = 1.53;
Octanol : water = 3;
Peanut oil : water = 117.

Solubility: *see* Table IV.

Table IV: Solubility of chlorocresol.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	Soluble
Alkali hydroxide solutions	Soluble
Chloroform	Soluble
Ethanol	1 in 0.4
Ether	Soluble
Fixed oils	Soluble
Glycerin	Soluble
Terpenes	Soluble
Water	1 in 260[a] 1 in 50 at 100°C[a]

[a] Aqueous solubility is decreased in the presence of electrolytes, particularly sodium chloride, potassium chloride, and potassium sulfonate.(6)

Vapor pressure: 0.008 kPa at 20°C;
0.67 kPa at 100°C.

11 Stability and Storage Conditions

Chlorocresol is stable at room temperature but is volatile in steam. Aqueous solutions may be sterilized by autoclaving. On exposure to air and light, aqueous solutions may become yellow colored. Solutions in oil or glycerin may be sterilized by heating at 160°C for 1 hour. The bulk material should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

Chlorocresol can decompose on contact with strong alkalis, evolving heat and fumes that ignite explosively. It is also incompatible with oxidizing agents, copper, and with solutions of calcium chloride, codeine phosphate, diamorphine hydrochloride, papaveretum, and quinine hydrochloride.(7) Discoloration also occurs with iron salts. Chlorocresol additionally exhibits strong sorption or binding tendencies to organic materials such as rubber, certain plastics, and nonionic surfactants.(8–11)

Chlorocresol may be lost from solutions to rubber closures, and in contact with polyethylene may initially be rapidly removed by sorption and then by permeation, the uptake being temperature dependent. Presoaking of components may reduce losses due to sorption, but not those by permeation.(12,13) Chlorocresol may also be taken up by polymethylmethacrylate and by cellulose acetate. Losses to polypropylene or rigid polyvinyl chloride are usually small.(14)

At a concentration of 0.1%, chlorocresol may be completely inactivated in the presence of nonionic surfactants, such as polysorbate 80.(9) However, other studies have suggested an enhancement of antimicrobial properties in the presence of surfactants.(15)(16) Bactericidal activity is also reduced, due to binding, by cetomacrogol, methylcellulose, pectin, or cellulose derivatives.(9,11) In emulsified or solubilized systems, chlorocresol readily partitions into the oil phase, particularly into vegetable oils and higher concentrations will be required for efficient preservation.(10,17)

13 Method of Manufacture

Chlorocresol is prepared by the chlorination of *m*-cresol.

14 Safety

Chlorocresol is used primarily as a preservative in topical pharmaceutical formulations but has also been used in nebulized solutions(18) and ophthalmic and parenteral preparations. It should not, however, be used in formulations for intrathecal, intracisternal, or peridural injection.

Chlorocresol is metabolized by conjugation with glucuronic acid and sulfate and is excreted in the urine, mainly as the conjugate, with little chlorocresol being excreted unchanged.

Although less toxic than phenol, chlorocresol may be irritant to the skin, eyes, and mucous membranes and has been reported to cause some adverse reactions when used as an excipient.(19,20)

Sensitization reactions may follow the prolonged application of strong solutions to the skin, although patch tests have shown that chlorocresol is not a primary irritant at concentrations up to 0.2%. Cross sensitization with the related preservative chloroxylenol has also been reported.(21)(22) At concentrations of 0.005% w/v, chlorocresol has been shown to produce a reversible reduction in the ciliary movement of human nasal epithelial cells *in vitro*; and at concentrations of 0.1% chlorocresol produces irreversible ciliostasis; therefore it should be used with caution in nasal preparations.(23) However, a clinical study in asthma patients challenged with chlorocresol or saline concluded that preservative might be used safely in nebulizer solution.(18)

Chlorocresol at a concentration as low as 0.05% produces ocular irritation in rabbits.(20) Despite such reports, chlorocresol has been tested in ophthalmic preparations.(24,25)

When used systemically, notably in a heparin injection preserved with chlorocresol 0.15%, delayed irritant and hypersensitivity reactions attributed to chlorocresol have been reported.(26,27) *See also* Section 19.

LD_{50} (mouse, IV): 0.07 g/kg(28)
LD_{50} (mouse, oral): 0.6 g/kg

LD_{50} (mouse, SC): 0.36 g/kg
LD_{50} (rabbit, dermal): >5 g/kg
LD_{50} (rat, dermal): >2 g/kg
LD_{50} (rat, oral): 1.83 g/kg
LD_{50} (rat, SC): 0.4 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Chlorocresol can be irritant to the skin, eyes, and mucous membranes. Eye protection, gloves, and protective clothing are recommended. Chlorocresol presents a slight fire hazard when exposed to heat or flame. It burns to produce highly toxic fumes containing phosgene and hydrogen chloride.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (topical creams and emulsions). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Cresol; chloroxylenol.

18 Comments

Chlorocresol has a characteristic odor which is difficult to mask in formulations, even at concentrations of 0.05–0.1%.

Although used in Europe, chlorocresol is not used in the USA in parenteral formulations. Chlorocresol has also been used as an experimental *in vitro* diagnostic agent for the diagnosis of hyperthermia.(29)

The EINECS number for chlorocresol is 200-431-6.

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21 Authors

S Nema.

22 Date of Revision

27 August 2005.

Chlorodifluoroethane (HCFC)

1 Nonproprietary Names

None adopted.

2 Synonyms

1,1-Difluoro-1-chloroethane; *Dymel 142b*; *Genetron 142b*; HCFC 142b; P-142b; propellant 142b; refrigerant 142b; *Solkane 142b*.

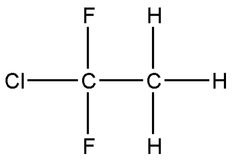
3 Chemical Name and CAS Registry Number

1-Chloro-1,1-difluoroethane [75-68-3]

4 Empirical Formula and Molecular Weight

$C_2H_3ClF_2$ 100.50

5 Structural Formula



6 Functional Category

Aerosol propellant.

7 Applications in Pharmaceutical Formulation or Technology

Chlorodifluoroethane is a hydrochlorofluorocarbon (HCFC) aerosol propellant previously used in topical pharmaceutical formulations. However, it is no longer permitted for use in pharmaceutical formulations because its harmful effects on the environment. It was also generally used in conjunction with difluoroethane to form a propellant blend with a specific gravity of 1. Chlorodifluoroethane was also used in combination with chlorodifluoromethane and hydrocarbon propellants. Chlorodifluoroethane may be used as a vehicle for dispersions and emulsions.

8 Description

Chlorodifluoroethane is a liquefied gas and exists as a liquid at room temperature when contained under its own vapor pressure, or as a gas when exposed to room temperature and atmospheric pressure. The liquid is practically odorless and colorless. Chlorodifluoroethane is noncorrosive and nonirritating.

9 Pharmacopeial Specifications

—

10 Typical Properties

Autoignition temperature: 632°C
Boiling point: -9.8°C
Critical temperature: 137.1°C
Density:
1.11 g/cm^3 for liquid at 25°C;
1.03 g/cm^3 for liquid at 54.5°C.
Flammability: flammable. Limits of flammability 6.2–17.9% v/v in air.
Melting point: -131°C
Solubility: soluble 1 in 715 parts of water at 20°C.
Vapor density (absolute): 4.487 g/m^3 at standard temperature and pressure.
Vapor density (relative): 3.48 (air = 1)
Vapor pressure:
339 kPa (49.2 psia) at 25°C (29.1 psig at 21.1°C);
772 kPa (112.0 psia) at 54.5°C.
Viscosity (dynamic): 0.33 mPa s (0.33 cP) for liquid at 21°C.

11 Stability and Storage Conditions

Chlorodifluoroethane is a nonreactive and stable material. The liquefied gas is stable when used as a propellant and should be stored in a metal cylinder in a cool, dry place.

12 Incompatibilities

Compatible with the usual ingredients used in the formulation of pharmaceutical aerosols. Chlorodifluoroethane can react vigorously with oxidizing materials.

13 Method of Manufacture

Chlorodifluoroethane is prepared by the chlorination of difluoroethane in the presence of a suitable catalyst; hydrochloric acid is also formed. The chlorodifluoroethane is purified to remove all traces of water and hydrochloric acid, as well as traces of the starting and intermediate materials.

14 Safety

Chlorodifluoroethane is no longer permitted for use as an aerosol propellant in topical pharmaceutical formulations. It is generally regarded as an essentially nontoxic and nonirritant material.

Deliberate inhalation of excessive quantities of chlorofluorocarbon propellant may result in death, and the following 'warning' statements must appear on the label of all aerosols:

> WARNING: Avoid inhalation. Keep away from eyes or other mucous membranes.

(Aerosols designed specifically for oral and nasal inhalation need not contain this statement.)

> WARNING: Do not inhale directly; deliberate inhalation of contents can cause death.

or

> WARNING: Use only as directed; intentional misuse by deliberately concentrating and inhaling the contents can be harmful or fatal.

Additionally, the label should contain the following information:

> WARNING: Contents under pressure. Do not puncture or incinerate container. Do not expose to heat or store at room temperature above 120°F (49°C). Keep out of the reach of children.

In the USA, the Environmental Protection Agency (EPA) additionally requires the following information on all aerosols containing chlorofluorocarbons as the propellant:

> WARNING: Contains a chlorofluorocarbon that may harm the public health and environment by reducing ozone in the upper atmosphere.

15 Handling Precautions

Chlorodifluoroethane is usually encountered as a liquefied gas and appropriate precautions for handling such materials should be taken. Eye protection, gloves, and protective clothing are recommended. Chlorodifluoroethane should be handled in a well-ventilated environment. Chlorofluorocarbon vapors are heavier than air and do not support life; therefore, when cleaning large tanks that have contained chlorofluorocarbons, adequate provisions for oxygen supply in the tanks must be made in order to protect workers cleaning the tanks.

Chlorodifluoroethane is flammable; *see* Section 10. When heated to decomposition, chlorodifluoroethane emits toxic fumes.

16 Regulatory Status

—

17 Related Substances

Chlorodifluoromethane.

Chlorodifluoromethane

Empirical formula: $CHClF_2$
Molecular weight: 86.47
CAS number: [75-45-6]
Synonyms: *Arcton 22*; difluorochloromethane; *Dyriel 22*; *Frigen 22*; HCFC 22; *Isceon 22*; P-22; propellant 22; refrigerant 22.
Boiling point: –40.8°C
Critical temperature: 96°C
Density: 1.19 g/cm^3 for liquid at 25°C.
Melting point: –146°C
Solubility: freely soluble in acetone, chloroform, and ether; soluble 1 in 330 parts of water at 25°C.
Vapor density (absolute): 3.860 g/cm^3 at standard temperature and pressure.
Vapor density (relative): 2.98 (air = 1)
Vapor pressure:
1041 kPa (151 psia) at 25°C;
2137 kPa (310 psia) at 54.5°C.
Handling precautions: the long-term exposure limit (8-hour TWA) for chlorodifluoromethane is 3590 mg/m^3 (1000 ppm).(1)
Comments: chlorodifluoromethane is a hydrochlorofluorocarbon (HCFC) aerosol propellant used in topical pharmaceutical formulations.

18 Comments

For a discussion of the numerical nomenclature applied to this aerosol propellant, *see* Chlorofluorocarbons.

19 Specific References

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22 Date of Revision

23 August 2005.

Chlorofluorocarbons (CFC)

(a) Dichlorodifluoromethane (Propellant 12)
(b) Dichlorotetrafluoroethane (Propellant 114)
(c) Trichloromonofluoromethane (Propellant 11)

1 Nonproprietary Names

(a) USPNF: Dichlorodifluoromethane
(b) USPNF: Dichlorotetrafluoroethane
(c) USPNF: Trichloromonofluoromethane

2 Synonyms

Arcton; *Dymel*; *Freon*; *Frigen*; *Genetron*; *Halon*; *Isceon*; *Isotron*.

Commonly also known as propellant-*x* or refrigerant-*x* (where *x* is 12, 114, or 11, for (a), (b), or (c), respectively).

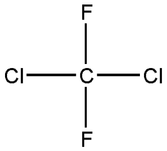
3 Chemical Name and CAS Registry Number

(a) Dichlorodifluoromethane [75-71-8]
(b) 1,2-Dichloro-1,1,2,2-tetrafluoroethane [76-14-2]
(c) Trichlorofluoromethane [75-69-4]

4 Empirical Formula and Molecular Weight

(a) CCl_2F_2	120.91
(b) $C_2Cl_2F_4$	170.92
(c) CCl_3F	137.37

5 Structural Formula



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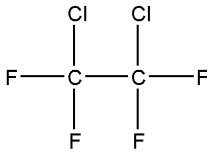

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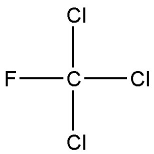

(c)

6 Functional Category

Aerosol propellants.

7 Applications in Pharmaceutical Formulation or Technology

Dichlorodifluoromethane, dichlorotetrafluoroethane, and trichloromonofluoromethane are chlorofluorocarbon (CFC) aerosol propellants used in pharmaceutical formulations.

Dichlorodifluoromethane is used as an aerosol propellant in metered-dose inhaler (MDI) formulations, either as the sole propellant or in combination with dichlorotetrafluoroethane, trichloromonofluoromethane, or mixtures of these chlorofluorocarbons. Dichlorodifluoromethane may also be used as a propellant in an aerosolized sterile talc used for intrapleural administration and is also used alone in some MDIs containing a steroid.

Dichlorotetrafluoroethane is used in combination with dichlorodifluoromethane, and in several cases with dichlorodifluoromethane and trichloromonofluoromethane, as the propellant in metered-dose oral and nasal aerosols.

Trichloromonofluoromethane is used in combination with dichlorodifluoromethane as the propellant in metered-dose inhaler aerosols. It is also used in combination with dichlorotetrafluoroethane and dichlorodifluoromethane.

These three propellants may be blended to obtain suitable solubility characteristics for MDIs when formulated as solutions. They will produce suitable vapor pressures so that optimum particle-size distribution as well as suitable respiratory fractions may be achieved.

Blends of trichloromonofluoromethane and dichlorodifluoromethane (propellant 11/12) or propellant 11/114/12 produce vapor pressures of 103–484 kPa (15–70 psig) at 21°C, which adequately cover the range of pressures required to produce the proper particle-size distribution for satisfactory aerosol products. Trichloromonofluoromethane is unique among the chlorofluorocarbon propellants in that it is a liquid at room temperature and atmospheric pressure and can be used to prepare a slurry with insoluble medicinal agents.

8 Description

Dichlorodifluoromethane is a liquefied gas and exists as a liquid at room temperature when contained under its own vapor pressure, or as a gas when exposed to room temperature and atmospheric pressure. The liquid is practically odorless and colorless. The gas in high concentrations has a faint etherlike odor. Dichlorodifluoromethane is noncorrosive, nonirritating, and nonflammable.

Dichlorotetrafluoroethane is a colorless, nonflammable liquefied gas with a faint, ethereal odor.

Trichloromonofluoromethane is a clear, volatile liquid at room temperature and atmospheric pressure. It has a characteristic carbon tetrachloride-like odor and is nonirritating and nonflammable.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications from USPNF 23.

Test	Propellant 12	Propellant 114	Propellant 11
Identification	+	+	+
Boiling temperature	–30°C	4°C	24°C
Water	$\leqslant$0.001%	$\leqslant$0.001%	$\leqslant$0.001%
High-boiling residues	$\leqslant$0.01%	$\leqslant$0.01%	$\leqslant$0.01%
Inorganic chlorides	+	+	+
Chromatographic purity	+	+	+
Assay	99.6–100.0%	99.6–100.0%	99.6–100.0%

10 Typical Properties

See Table II for selected typical properties.

11 Stability and Storage Conditions

Chlorofluorocarbon propellants are nonreactive and stable at temperatures up to 550°C. The liquefied gas is stable when used as a propellant and should be stored in a metal cylinder in a cool, dry place.

12 Incompatibilities

The presence of greater than 5% water in solutions that contain trichloromonofluoromethane may lead to hydrolysis of the propellant and the formation of traces of hydrochloric acid, which may be irritant to the skin or cause corrosion of metallic canisters. Trichloromonofluoromethane may also react with aluminum, in the presence of ethanol, to cause corrosion within a cylinder with the formation of hydrogen gas. Similarly, alcohols in the presence of trace amounts of oxygen, peroxides, or other free-radical catalysts may react with trichloromonofluoromethane to form trace quantities of hydrochloric acid.

Both dichlorodifluoromethane and dichlorotetrafluoroethane are compatible with most ingredients used in pharmaceutical aerosols. Because of their poor miscibility with water, most MDIs are formulated as suspensions. However, solution MDIs can be prepared through the use of ethanol as a cosolvent for water and propellant, resulting in a clear solution (provided the water content is less than 5%).

13 Method of Manufacture

Dichlorodifluoromethane is prepared by the reaction of hydrogen fluoride with carbon tetrachloride in the presence of a suitable catalyst, such as polyvalent antimony. The dichlorodifluoromethane formed is further purified to remove all traces of water and hydrochloric acid as well as traces of the starting and intermediate materials.

Trichloromonofluoromethane is also obtained by this process.

Dichlorotetrafluoroethane is prepared by the reaction of hydrogen fluoride with chlorine and perchloroethylene in the presence of a suitable catalyst such as polyvalent antimony.

14 Safety

Dichlorodifluoromethane, dichlorotetrafluoroethane, and trichloromonofluoromethane have been used for over 40 years as propellants in topical, oral, and nasal aerosol formulations and are generally regarded as nontoxic and nonirritant materials when used as directed.

The propellants used for metered-dose inhalant aerosol products generally vaporize quickly and most of the vapors escape and are not inhaled. However, a small amount of the propellant may be inhaled with the active ingredient and be carried to the respiratory system. These amounts of propellant

Table II: Selected typical properties for chlorofluorocarbon propellants.

Test	Propellant 12	Propellant 114	Propellant 11
Boiling point	−29.8°C	4.1°C	23.7°C
Critical pressure	4.01 MPa (39.6 atm)	3268 kPa (474 psia)	4.38 MPa (43.2 atm)
Critical temperature	111.5°C	145.7°C	198°C
Density			
Liquid at 21°C	1.325 g/cm^3	1.468 g/cm^3	1.485 g/cm^3
Liquid at 54.5°C	1.191 g/cm^3	1.360 g/cm^3	1.403 g/cm^3
Flammability	Nonflammable	Nonflammable	Nonflammable
Freezing point	−158°C	−94°C	−111°C
Kauri-butanol value	18	12	60
Solubility at 20°C (unless otherwise stated)			
Ethanol (95%)	Soluble	Soluble	Soluble
Ether	Soluble	Soluble	Soluble
Water	1 in 3570 at 25°C	1 in 7690 at 25°C	1 in 909 at 25°C
Surface tension at 25°C	9 mN/m (9 dynes/cm)	13 mN/m (13 dynes/cm)	19 mN/m (19 dynes/cm)
Vapor density			
Absolute	5.398 g/m^3	7.63 g/m^3	6.133 g/m^3
Relative	4.19 (air = 1)	5.92 (air = 1)	5.04 (air = 1)
Vapor pressure			
At 21°C	585.4 kPa (84.9 psia)	190.3 kPa (27.6 psia)	92.4 kPa (13.4 psia)
At 54.5°C	1351.4 kPa (196.0 psia)	506.8 kPa (73.5 psia)	268.9 kPa (39.0 psia)
Viscosity (dynamic)			
Liquid at 21°C	0.262 mPa s (0.262 cP)	0.386 mPa s (0.386 cP)	0.439 mPa s (0.439 cP)
Liquid at 54.5°C	0.227 mPa s (0.227 cP)	0.296 mPa s (0.296 cP)	0.336 mPa s (0.336 cP)

do not present a toxicological problem and are quickly cleared from the lungs. Deliberate inhalation of excessive quantities of fluorocarbon propellant may result in death, and the following 'warning' statements must appear on the label of all aerosols:

> WARNING: Avoid inhalation. Keep away from eyes or other mucous membranes.

(Aerosols designed specifically for oral inhalation need not contain this statement).

> WARNING: Do not inhale directly; deliberate inhalation of contents can cause death.

> or

> WARNING: Use only as directed; intentional misuse by deliberately concentrating and inhaling the contents can be harmful or fatal.

Additionally, the label should contain the following information:

> WARNING: Contents under pressure. Do not puncture or incinerate container. Do not expose to heat or store at room temperature above 120°F (49°C). Keep out of the reach of children.

In the USA, the Environmental Protection Agency (EPA) additionally requires the following information on all aerosols containing chlorofluorocarbons as the propellant:

> WARNING: Contains a chlorofluorocarbon that may harm the public health and environment by reducing ozone in the upper atmosphere.

(Metered-dose inhalers are exempt from this regulation.)

15 Handling Precautions

Dichlorodifluoromethane and dichlorotetrafluoroethane are usually encountered as a liquefied gas and appropriate precautions for handling such materials should be taken. Eye protection, gloves, and protective clothing are recommended. These propellants should be handled in a well-ventilated environment. Chlorofluorocarbon vapors are heavier than air and do not support life; therefore, when cleaning large tanks that have contained chlorofluorocarbons, adequate provisions for supply of oxygen in the tanks must be made in order to protect workers cleaning the tanks.

Although nonflammable, when heated to decomposition chlorofluorocarbons emit toxic fumes containing phosgene and fluorides. Although not as volatile as dichlorodifluoroethane or dichlorotetrafluoroethane, trichloromonofluoromethane should be handled as indicated above. Since it is a liquid at room temperature, caution should be exercised in handling this material to prevent spillage onto the skin. It is an irritant to the eyes.

The long-term exposure limit (8-hour TWA) for dichlorodifluoromethane is 5030 mg/m^3 (1000 ppm). The short-term exposure limit (15-minute) is 6280 mg/m^3 (1250 ppm).(1)

The long-term exposure limit (8-hour TWA) for dichlorotetrafluoroathane is 7110 mg/m^3 (1000 ppm). The short-term exposure limit (15-minute) is 8890 mg/m^3 (1250 ppm).(1)

The long-term exposure limit (8-hour TWA) for trichlorofluoromethane is 5710 mg/m^3 (1000 ppm). The short-term exposure limit (15-minute) is 7140 mg/m^3 (1250 ppm).(1)

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (aerosol formulations for inhalation, nasal, oral, and topical applications). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

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18 Comments

Fluorocarbon (FC) aerosol propellants may be identified by a standardized numbering nomenclature; for example, dichlorodifluoromethane is known as propellant 12, while dichlorotetrafluoroethane is known as propellant 114.

Usually, three digits are used to describe the propellant, except when the first digit would be zero, in which case only two digits are used. The first digit is one less than the number of carbon atoms in the molecule. Thus, if the molecule is a methane derivative the first digit would be zero (1 – 1) and is ignored, so that only two digits are used in the propellant description; e.g. propellant 12. For an ethane derivative, the first digit would be a one (2 – 1); e.g. propellant 114.

The second digit is one more than the number of hydrogen atoms in the molecule, while the third digit represents the number of fluorine atoms in the molecule. The difference between the sum of the fluorine and hydrogen atoms and the number of atoms required to saturate the carbon chain is the number of chlorine atoms in the molecule. Isomers of a compound have the same identifying number and an additional letter; a, b, c, and so on. Cyclic derivatives are indicated by the letter C before the identifying number. With unsaturated propellants, the number 1 is used as the fourth digit from the right to indicate an unsaturated double bond.

Thus for dichlorodifluoromethane (propellant 12):

First digit = 0 signifies number of C atoms = 1
Second digit = 1 signifies number of H atoms = 0
Third digit = 2 signifies number of F atoms = 2
Number of Cl atoms = 4 – (2 – 0) = 2

Under the terms of the Montreal Protocol, aimed at reducing damage to the ozone layer, the use of chlorofluorocarbons, including dichlorodifluoromethane, dichlorotetrafluoroethane, and trichloromonofluoromethane, has been prohibited from January 1996.(2–6) However, this prohibition does not apply to essential uses such as existing pharmaceutical formulations for which no alternative chlorofluorocarbon-free product is available. New pharmaceutical formulations containing chlorofluorocarbons may also be exempted provided they demonstrate that there is no technically feasible alternative to their use, that the product is of a substantial health benefit, and that its use would not involve release of significant quantities of chlorofluorocarbon into the atmosphere. The EPA and FDA approved essential-use status for dichlorodifluoromethane for a sterile aerosol talc used in the treatment of malignant pleural effusion in patients with lung cancer. Regulatory bodies in individual countries should be consulted for advice on chlorofluorocarbon use in MDI formulations.

Essential-use allowances are allocated in the USA by the Environmental Protection Agency following approval of the 'Parties to the Montreal Protocol on Substances that Deplete the Ozone Layer'. These allocations are made for a specified essential use and cannot be used for other essential uses, traded, or sold. This allows for the continued sale of existing exempted MDIs and other products designated as an essential use. These allocations are granted on an annual basis. Both the EPA and the FDA have proposed rules for the eventual elimination of CFC-containing MDIs. The development of CFC-free MDIs has been slow and time-consuming. Albuterol-containing CFC-free MDIs are available in the USA, the UK, and Germany, as well as most other countries of the world. A CFC-free MDI containing beclomethasone dipropionate has also been approved for sale in the UK and USA. In June 2004 the FDA proposed the near-term elimination of the essential use designation for albuterol MDI. The eventual elimination of the essential use exemption is required as part of the United States' general obligations under the Montreal Protocol. Additionally, there is a more immediate requirement for an action plan that includes a specific end-date for essential use exemptions for CFCs for albuterol MDIs. A phase-out date has been proposed for 2010.(7) *See* Tetrafluoroethane and Heptafluoropropane for further details.

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21 Authors

CJ Sciarra, JJ Sciarra.

22 Date of Revision

23 August 2005.

Chloroxylenol

1 Nonproprietary Names

BP: Chloroxylenol
USP: Chloroxylenol

2 Synonyms

4-Chloro-3,5-dimethylphenol; *Nipacide PX*; parachlorometaxylenol; *p*-chloro-*m*-xylenol; PCMX.

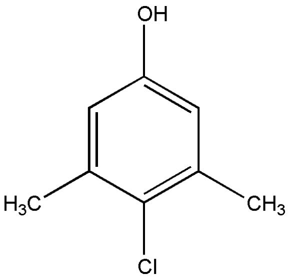
3 Chemical Name and CAS Registry Number

4-Chloro-3,5-xylenol [88-04-0]

4 Empirical Formula and Molecular Weight

C_8H_9ClO 156.61

5 Structural Formula



6 Functional Category

Antimicrobial preservative; antiseptic; disinfectant.

7 Applications in Pharmaceutical Formulation or Technology

Chloroxylenol is a common constituent of many proprietary disinfectants used for skin and wound disinfection; *see* Table I.

As a pharmaceutical excipient, chloroxylenol is commonly used in low concentrations as an antimicrobial preservative in topical formulations such as creams and ointments. Chloroxylenol is also used in a number of cosmetic formulations.

Therapeutically, chloroxylenol has been investigated as a treatment for acne vulgaris,(1) and also for treating infected root canals.(2)

Table I: Uses of chloroxylenol.

Use	Concentration (%)
Antiseptic powder	0.5
Antimicrobial preservative for otic and topical preparations	0.1–0.8
Disinfectant	2.5–5.0

8 Description

White or cream-colored crystals or crystalline powder with a characteristic phenolic odor. Volatile in steam.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for chloroxylenol.

Test	BP 2004	USP 28
Identification	+	+
Characters	+	—
Residue on ignition	—	⩽0.1%
Water	—	⩽0.5%
Iron	—	⩽0.01%
Melting range	114–116°C	114–116°C
Related substances	+	+
Assay	98.0–103.0%	⩾98.5%

10 Typical Properties

Antimicrobial activity: chloroxylenol is effective against Gram-positive bacteria but less active against Gram-negative bacteria. The activity of chloroxylenol against Gram-negative bacilli can be increased by the addition of a chelating agent such as edetic acid.(3) Chloroxylenol is inactive against bacterial spores. Antimicrobial activity may be reduced by loss of chloroxylenol from a formulation due to incompatibilities with packaging materials or other excipients, such as nonionic surfactants.(4) Solution pH does not have a marked effect on the activity of chloroxylenol.(5)

Boiling point: 246°C

Melting point: 115.5°C

Solubility: freely soluble in ethanol (95%); soluble in ether, terpenes, and fixed oils; very slightly soluble in water. Dissolves in solutions of alkali hydroxides.

11 Stability and Storage Conditions

Chloroxylenol is stable at normal room temperature, but is volatile in steam. Contact with natural rubber should be avoided. Aqueous solutions of chloroxylenol are susceptible to microbial contamination and appropriate measures should be taken to prevent contamination during storage or dilution. Chloroxylenol should be stored in polyethylene, mild steel or stainless steel containers, which should be well-closed and kept in a cool, dry place.

12 Incompatibilities

Chloroxylenol has been reported to be incompatible with nonionic surfactants and methylcellulose.

13 Method of Manufacture

Chloroxylenol is prepared by treating 3,5-dimethylphenol with chlorine or sulfuryl chloride (SO_2Cl_2).

14 Safety

Chloroxylenol is generally regarded as a relatively nontoxic and nonirritant material when used as an excipient. However, allergic skin reactions have been reported.(6,7) Taken orally, chloroxylenol is mildly toxic and has been associated with isolated reports of fatal(8) or severe instances of self-poisoning.(9,10)

LD_{50} (mouse, IP): 0.115 g/kg(11)
LD_{50} (rat, oral): 3.83 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Chloroxylenol is an eye irritant and eye protection is recommended. When heated to decomposition, chloroxylenol emits toxic fumes.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (otic preparations; topical creams and emulsions). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Chlorocresol.

18 Comments

The EINECS number for chloroxylenol is 201-793-8.

19 Specific References

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21 Authors

LME McIndoe.

22 Date of Revision

24 August 2005.

Cholesterol

1 Nonproprietary Names

BP: Cholesterol
JP: Cholesterol
PhEur: Cholesterolum
USPNF: Cholesterol

2 Synonyms

Cholesterin; cholesterolum.

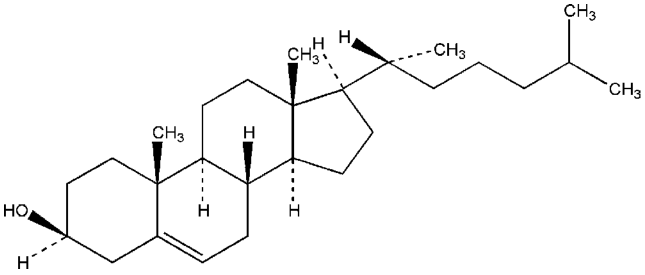
3 Chemical Name and CAS Registry Number

Cholest-5-en-3β-ol [57-88-5]

4 Empirical Formula and Molecular Weight

$C_{27}H_{46}O$ 386.67

5 Structural Formula



6 Functional Category

Emollient; emulsifying agent.

7 Applications in Pharmaceutical Formulation or Technology

Cholesterol is used in cosmetics and topical pharmaceutical formulations at concentrations of 0.3–5.0% w/w as an emulsifying agent. It imparts water-absorbing power to an ointment and has emollient activity.

Cholesterol also has a physiological role. It is the major sterol of the higher animals, and it is found in all body tissues, especially in the brain and spinal cord. It is also the main constituent of gallstones.

8 Description

Cholesterol occurs as white or faintly yellow, almost odorless, pearly leaflets, needles, powder, or granules. On prolonged exposure to light and air, cholesterol acquires a yellow to tan color.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for cholesterol.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Acidity	+	+	+
Characters	—	+	—
Clarity of solution	+	—	—
Loss on drying	⩽0.3%	⩽0.3%	⩽0.3%
Melting range	147–150°C	147–150°C	147–150°C
Organic volatile impurities	—	—	+
Residue on ignition	⩽0.10%	—	⩽0.1%
Solubility in alcohol	—	+	+
Specific rotation	–34° to –38°	—	–34° to –38°
Sulfated ash	—	⩽0.1%	—
Assay	—	95.0–97.0%	—

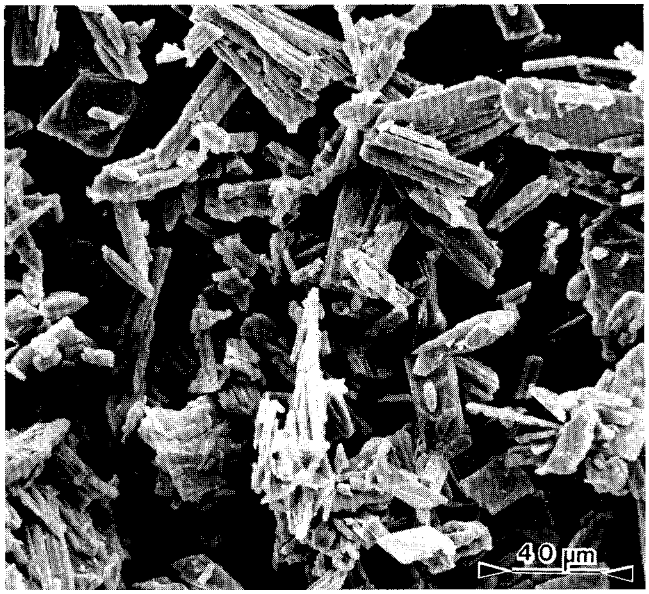
10 Typical Properties

Boiling point: 360°C
Density: 1.052 g/cm^3 for anhydrous form.
Dielectric constant D^{20}: 5.41
Melting point: 147–150°C
Solubility: *see* Table II.$^{(1-3)}$
Specific rotation $[\alpha]_D^{20}$:
−39.5° (2% w/v solution in chloroform);
−31.5° (2% w/v solution in ether).

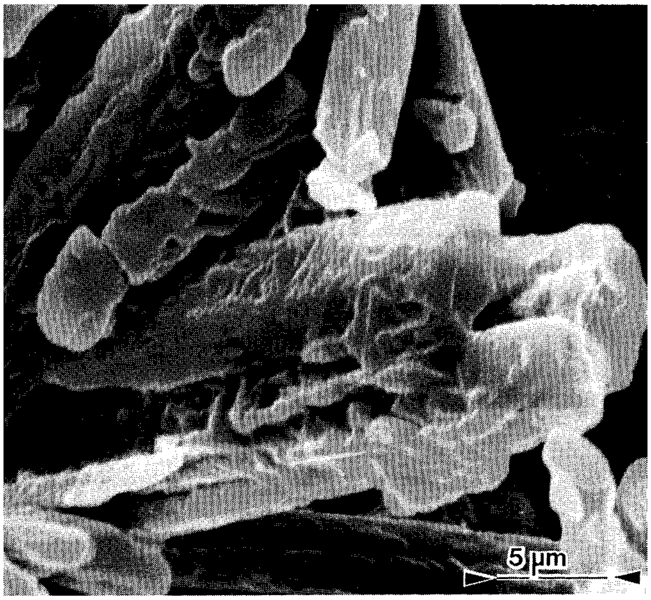
Table II: Solubility of cholesterol.

Solvent	Solubility at 20°C$^{(1-3)}$ unless otherwise stated
Acetone	Soluble
Benzene	1 in 7
Chloroform	1 in 4.5
Ethanol	1 in 147 at 0°C
	1 in 78 at 20°C
	1 in 29 at 40°C
	1 in 19 at 50°C
	1 in 13 at 60°C
Ethanol (95%)	1 in 78 (slowly)
	1 in 3.6 at 80°C
Ether	1 in 2.8
Hexane	1 in 52
Isopropyl myristate	1 in 19
Methanol	1 in 294 at 0°C
	1 in 153 at 20°C
	1 in 53 at 40°C
	1 in 34 at 50°C
	1 in 23 at 60°C
Vegetable oils	Soluble
Water	Practically insoluble

SEM: 1
Excipient: Cholesterol
Manufacturer: Pflatz & Bauer, Inc.
Magnification: 240×



SEM: 2
Excipient: Cholesterol
Manufacturer: Pfaltz & Bauer, Inc.
Magnification: 2400×



11 Stability and Storage Conditions

Cholesterol is stable and should be stored in a well-closed container, protected from light.

12 Incompatibilities

Cholesterol is precipitated by digitonin.

13 Method of Manufacture

The commercial material is normally obtained from the spinal cord of cattle by extraction with petroleum ethers, but it may also be obtained from wool fat. Purification is normally accomplished by repeated bromination. Cholesterol may also be produced by entirely synthetic means.(4)

Cholesterol produced from animal organs will always contain cholestanol and other saturated sterols.

See also Section 14.

14 Safety

Cholesterol is generally regarded as an essentially nontoxic and nonirritant material at the levels employed as an excipient.(3) It has, however, exhibited experimental teratogenic and reproductive effects, and mutation data have been reported.(5)

Cholesterol is often derived from animal sources and this must be done in accordance with the regulations for human consumption. The risk of bovine spongiform encephalopathy (BSE) contamination has caused some concern over the use of animal-derived cholesterol in pharmaceutical products.(6) However, synthetic methods of cholesterol manufacture have been developed.(4)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Rubber or plastic gloves, eye protection, and a respirator are recommended.

May be harmful following inhalation or ingestion of large quantities, or over prolonged periods of time, owing to the possible involvement of cholesterol in atherosclerosis and gallstones. May be irritant to the eyes. When heated to decomposition, cholesterol emits acrid smoke and irritating fumes.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (injections, ophthalmic, topical, and vaginal preparations).

Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Lanolin; lanolin alcohols; lanolin hydrous.

18 Comments

A novel cholesterol-based cationic lipid has been developed that promotes DNA transfer in cells.(7,8) Cholesterol monohydrate becomes anhydrous at 70–80°C.

The EINECS number for cholesterol is 200-353-2.

19 Specific References

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21 Authors

SC Owen.

22 Date of Revision

12 August 2005.

Citric Acid Monohydrate

1 Nonproprietary Names

BP: Citric acid monohydrate
JP: Citric acid
PhEur: Acidum citricum monohydricum
USP: Citric acid

2 Synonyms

E330; 2-hydroxypropane-1,2,3-tricarboxylic acid monohydrate.

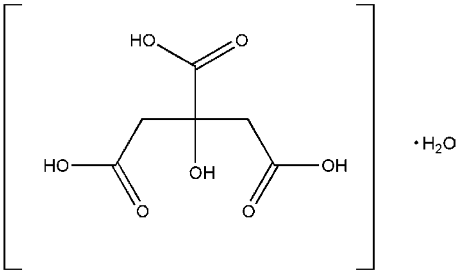
3 Chemical Name and CAS Registry Number

2-Hydroxy-1,2,3-propanetricarboxylic acid monohydrate [5949-29-1]

4 Empirical Formula and Molecular Weight

$C_6H_8O_7{\cdot}H_2O$ 210.14

5 Structural Formula



6 Functional Category

Acidifying agent; antioxidant; buffering agent; chelating agent; flavor enhancer.

7 Applications in Pharmaceutical Formulation or Technology

Citric acid (as either the monohydrate or anhydrous material) is widely used in pharmaceutical formulations and food products, primarily to adjust the pH of solutions. It has also been used experimentally to adjust the pH of tablet matrices in enteric-coated formulations for colon-specific drug delivery.(1) Citric acid monohydrate is used in the preparation of effervescent granules, while anhydrous citric acid is widely used in the preparation of effervescent tablets.(2–4) Citric acid has also been shown to improve the stability of spray-dried insulin powder in inhalation formulations.(5)

In food products, citric acid is used as a flavor enhancer for its tart, acidic taste. Citric acid monohydrate is used as a sequestering agent and antioxidant synergist; *see* Table I. It is also a component of anticoagulant citrate solutions. Therapeutically, preparations containing citric acid have been used to dissolve renal calculi.

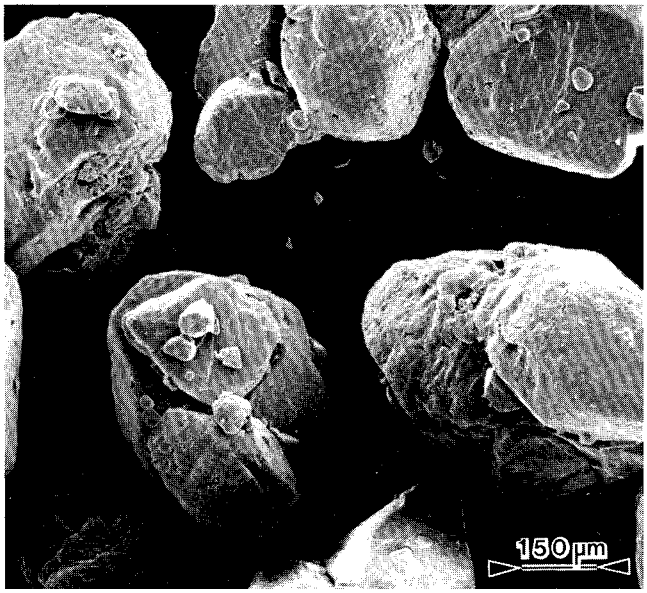
Table I: Uses of citric acid monohydrate.

Use	Concentration (%)
Buffer solutions	0.1–2.0
Flavor enhancer for liquid formulations	0.3–2.0
Sequestering agent	0.3–2.0

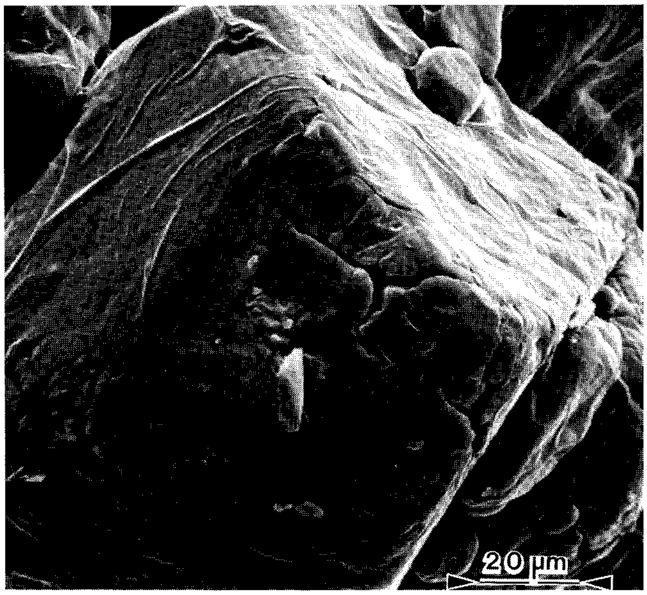
8 Description

Citric acid monohydrate occurs as colorless or translucent crystals, or as a white crystalline, efflorescent powder. It is odorless and has a strong acidic taste. The crystal structure is orthorhombic.

SEM: 1
Excipient: Citric acid monohydrate
Manufacturer: Pfizer Ltd.
Magnification: 60×



SEM: 2
Excipient: Citric acid monohydrate
Manufacturer: Pfizer Ltd.
Magnification: 600×



9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for citric acid monohydrate (and anhydrous).

Test	JP 2001	PhEur 2005	USP 28[a]
Identification	+	+	+
Characters	—	+	—
Appearance of solution	—	+	—
Water			
(hydrous form)	—	7.5–9.0%	⩽8.8%
(anhydrous form)	⩽0.5%	⩽1.0%	⩽0.5%
Bacterial endotoxins	—	+	—
Residue on ignition	⩽0.1%	—	⩽0.05%
Sulfated ash	—	⩽0.1%	—
Calcium	+	—	—
Aluminum	—	⩽0.2 ppm	—
Oxalate	+	—	+
Oxalic acid	—	⩽350 ppm	—
Sulfate	⩽0.048%	⩽150 ppm	+
Arsenic	⩽1 ppm	—	⩽3 ppm
Heavy metals	⩽10 ppm	⩽10 ppm	⩽0.001%
Related substances	+	—	—
Readily carbonizable substances	+	+	+
Polycyclic aromatic hydrocarbon	+	—	—
Organic volatile impurities	—	—	+
Assay (anhydrous basis)	⩾99.5%	99.5–101.0%	99.5–100.5%

[a] Note that the JP 2001 and PhEur 2005 have separate monographs for the monohydrate and anhydrous material; the USP 28 has a single monograph for both materials.

10 Typical Properties

Acidity/alkalinity: pH = 2.2 (1% w/v aqueous solution)
Dissociation constant:
pK_{a1}: 3.128 at 25°C;
pK_{a2}: 4.761 at 25°C;
pK_{a3}: 6.396 at 25°C.
Density: 1.542 g/cm^3
Heat of combustion: −1972 kJ/mol (−471.4 kcal/mol)
Heat of solution: −16.3 kJ/mol (−3.9 kcal/mol) at 25°C
Hygroscopicity: at relative humidities less than about 65%, citric acid monohydrate effloresces at 25°C, the anhydrous acid being formed at relative humidities less than about 40%. At relative humidities between about 65% and 75%, citric acid monohydrate absorbs insignificant amounts of moisture, but under more humid conditions substantial amounts of water are absorbed.
Melting point: ≈100°C (softens at 75°C)
Particle size distribution: various grades of citric acid monohydrate with different particle sizes are commercially available.
Solubility: soluble 1 in 1.5 parts of ethanol (95%) and 1 in less than 1 part of water; sparingly soluble in ether.
Viscosity (dynamic): 6.5 mPa s (6.5 cP) for a 50% w/v aqueous solution at 25°C.

See also Section 17.

11 Stability and Storage Conditions

Citric acid monohydrate loses water of crystallization in dry air or when heated to about 40°C. It is slightly deliquescent in moist air. Dilute aqueous solutions of citric acid may ferment on standing.

The bulk monohydrate or anhydrous material should be stored in airtight containers in a cool, dry place.

12 Incompatibilities

Citric acid is incompatible with potassium tartrate, alkali and alkaline earth carbonates and bicarbonates, acetates, and sulfides. Incompatibilities also include oxidizing agents, bases, reducing agents, and nitrates. It is potentially explosive in combination with metal nitrates. On storage, sucrose may crystallize from syrups in the presence of citric acid.

13 Method of Manufacture

Citric acid occurs naturally in a number of plant species and may be extracted from lemon juice, which contains 5–8% citric acid, or pineapple waste. Anhydrous citric acid may also be produced industrially by mycological fermentation of crude sugar solutions such as molasses, using strains of *Aspergillus niger.* Citric acid is purified by recrystallization; the anhydrous form is obtained from a hot concentrated aqueous solution and the monohydrate from a cold concentrated aqueous solution.

14 Safety

Citric acid is found naturally in the body, mainly in the bones, and is commonly consumed as part of a normal diet. Orally ingested citric acid is absorbed and is generally regarded as a nontoxic material when used as an excipient. However, excessive or frequent consumption of citric acid has been associated with erosion of the teeth.(6)

Citric acid and citrates also enhance intestinal aluminum absorption in renal patients, which may lead to increased, harmful serum aluminum levels. It has therefore been suggested that patients with renal failure taking aluminum compounds to control phosphate absorption should not be prescribed citric acid or citrate-containing products.[7]

See Section 17 for anhydrous citric acid animal toxicity data.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Direct contact with eyes can cause serious damage. Citric acid should be handled in a well-ventilated environment or a dust mask should be worn.

16 Regulatory Status

GRAS listed. The anhydrous form is accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (inhalations; IM, IV, and other injections; ophthalmic preparations; oral capsules, solutions, suspensions and tablets; topical and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in Japan and the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Anhydrous citric acid; fumaric acid; malic acid; sodium citrate dihydrate; tartaric acid.

Anhydrous citric acid

Empirical formula: $C_6H_8O_7$
Molecular weight: 192.12
CAS number: [77-92-9]
Synonyms: acidum citricum anhydricum; citric acid; E330; 2-hydroxy-β-1,2,3-propanetricarboxylic acid; 2-hydroxypropane 1,2,3-tricarboxylic acid.
Appearance: odorless or almost odorless, colorless crystals or a white crystalline powder. Crystal structure is monoclinic holohedral.
Dissociation constants:
pK_{a1}: 3.128 at 25°C;
pK_{a2}: 4.761 at 25°C;
pK_{a3}: 6.396 at 25°C.
Density: 1.665 g/cm^3
Heat of combustion: –1985 kJ/mol (–474.5 kcal/mol)
Hygroscopicity: at relative humidities between about 25–50%, anhydrous citric acid absorbs insignificant amounts of water at 25°C. However, at relative humidities between 50% and 75%, it absorbs significant amounts, with the monohydrate being formed at relative humidities approaching 75%. At relative humidities greater than 75% substantial amounts of water are absorbed by the monohydrate.
Melting point: 153°C
Solubility: soluble 1 in 1 part of ethanol (95%) and 1 in 1 of water; sparingly soluble in ether.
Safety:
LD_{50} (mouse, IP): 0.9 g/kg[8]
LD_{50} (mouse, IV): 0.04 g/kg
LD_{50} (mouse, oral): 5.04 g/kg
LD_{50} (mouse, SC): 2.7 g/kg
LD_{50} (rabbit, IV): 0.33 g/kg
LD_{50} (rat, IP): 0.88 g/kg
LD_{50} (rat, oral): 3.0 g/kg
LD_{50} (rat, SC): 5.5 g/kg
Comments: the EINECS number for anhydrous citric acid is 201-069-1.

18 Comments

A specification for citric acid monohydrate is contained in the Food Chemicals Codex (FCC).

The EINECS number for citric acid monohydrate is 201-069-1.

19 Specific References

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21 Authors

GE Amidon.

22 Date of Revision

8 August 2005.

Colloidal Silicon Dioxide

1 Nonproprietary Names

BP: Colloidal anhydrous silica
PhEur: Silica colloidalis anhydrica
USPNF: Colloidal silicon dioxide

2 Synonyms

Aerosil; *Cab-O-Sil*; *Cab-O-Sil M-5P*; colloidal silica; fumed silica; light anhydrous silicic acid; silicic anhydride; silicon dioxide fumed; *Wacker HDK*.

3 Chemical Name and CAS Registry Number

Silica [7631-86-9]

4 Empirical Formula and Molecular Weight

SiO_2 60.08

5 Structural Formula

SiO_2

6 Functional Category

Adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products; *see* Table I. Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting.(1–3)

Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations.(4) With other ingredients of similar refractive index, transparent gels may be formed. The degree of viscosity increase depends on the polarity of the liquid (polar liquids generally require a greater concentration of colloidal silicon dioxide than nonpolar liquids). Viscosity is largely independent of temperature. However, changes to the pH of a system may affect the viscosity; *see* Section 11.

In aerosols, other than those for inhalation, colloidal silicon dioxide is used to promote particulate suspension, eliminate hard settling, and minimize the clogging of spray nozzles. Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders.(5) Colloidal silicon dioxide is frequently added to suppository formulations containing lipophilic excipients to increase viscosity, prevent sedimentation during molding, and decrease the release rate.(6,7) Colloidal silicone dioxide is also used as an adsorbent during the preparation of wax microspheres;(8) as a thickening agent for topical preparations;(9) and has been used to aid the freeze-drying of nanocapsules and nanosphere suspensions.(10)

Table I: Uses of colloidal silicon dioxide.

Use	Concentration (%)
Aerosols	0.5–2.0
Emulsion stabilizer	1.0–5.0
Glidant	0.1–0.5
Suspending and thickening agent	2.0–10.0

8 Description

Colloidal silicon dioxide is a submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, nongritty amorphous powder.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for colloidal silicon dioxide.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
pH (4% w/v dispersion)	3.5–5.5	3.5–5.5
Arsenic	—	⩽8 μg/g
Chloride	⩽250 ppm	—
Heavy metals	⩽25 ppm	—
Loss on drying	—	⩽2.5%
Loss on ignition	⩽5.0%	⩽2.0%
Organic volatile impurities	—	+
Assay (on ignited sample)	99.0–100.5%	99.0–100.5%

10 Typical Properties

Acidity/alkalinity: pH = 3.5–4.4 (4% w/v aqueous dispersion)
Density (bulk): 0.029–0.042 g/cm^3
Density (tapped): *See* Tables III, IV and V.
Flowability: 35.52% (Carr compressibility index)
Moisture content: *See* Figure 1.(11,12)
Particle size distribution: 7–16 nm. *See also* Figure 2.
Refractive index: 1.46
Solubility: practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water.
Specific gravity: 2.2

Specific surface area: 200–400 m^2/g (Stroehlein apparatus, single point); 50–380 m^2/g (BET method). *See also* Tables III, IV and V.

Several grades of colloidal silicon dioxide are commercially available, which are produced by modifying the manufacturing process. The modifications do not affect the silica content, specific gravity, refractive index, color, or amorphous form. However, particle size, surface areas, and densities are affected. The physical properties of three commercially available colloidal silicon dioxides, *Aerosil* (Degussa), *Cab-O-Sil* (Cabot Corporation), and *Wacker HDK* (Wacker-Chemie GmbH) are shown in Tables III, IV and V, respectively.

Table III: Physical properties of *Aerosil.*

Grade	Specific surface area(a) (m^2/g)	Density (tapped) (g/cm^3)
130	130 ± 25	0.05
130vs	130 ± 25	0.12
200	200 ± 25	0.05
200vs	200 ± 25	0.12
300	300 ± 30	0.05
380	380 ± 30	0.05

(a) BET method.

Table IV: Physical properties of *Cab-O-Sil.*(13)

Grade	Specific surface area(a) (m^2/g)	Density (tapped) (g/cm^3)
LM-5	130 ± 25	0.04
LM-50	150 ± 25	0.04
M-5	200 ± 25	0.04
H-5	325 ± 25	0.04
EH-5	390 ± 40	0.04
M-7D	200 ± 25	0.10

(a) BET method.

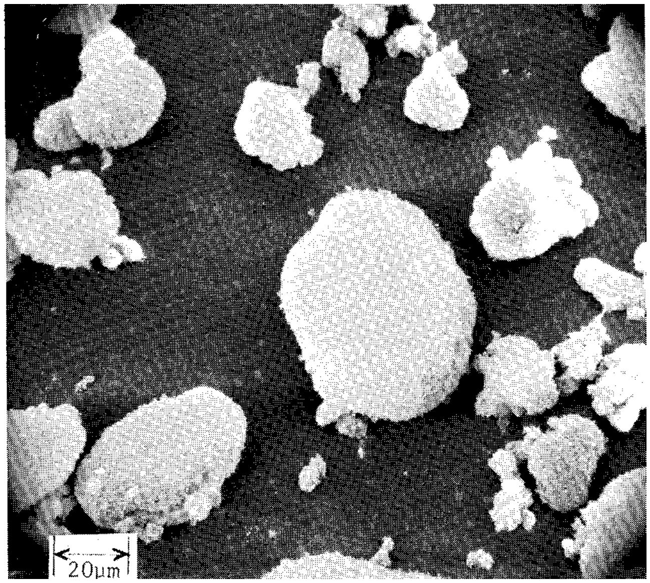
Table V: Physical properties of *Wacker HDK.*(14)

Grade	Specific surface area(a) (m^2/g)	Density (tapped) (g/cm^3)
S13	125 ± 15	0.05
V15	150 ± 20	0.05
N20	200 ± 30	0.04
T30	300 ± 30	0.04
T40	400 ± 40	0.04
H15	120 ± 20	0.04
H20	170 ± 30	0.04
H30	250 ± 30	0.04
H2000	140 ± 30	0.22
H3004	210 ± 30	0.08
H2015	110 ± 30	0.20
H2050	110 ± 30	0.20

(a) BET method.

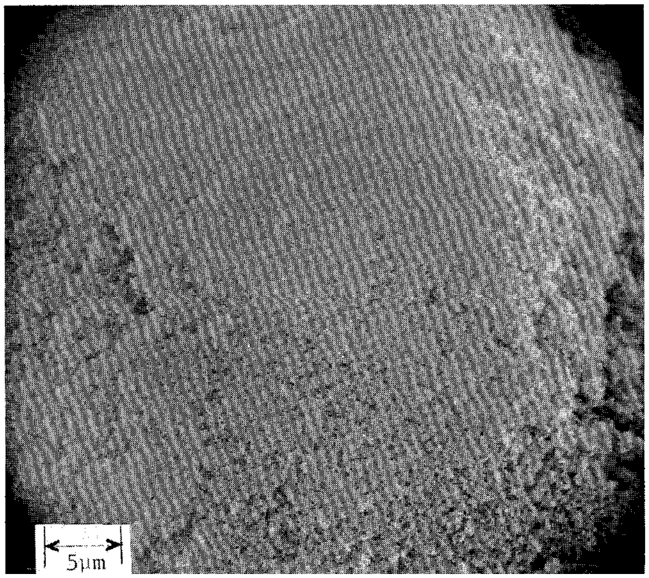
SEM: 1

Excipient: Colloidal silicon dioxide (*Aerosil A-200*)
Manufacturer: Degussa
Lot No.: 87A-1 (04169C)
Magnification: 600×
Voltage: 20 kV



SEM: 2

Excipient: Colloidal silicon dioxide (*Aerosil A-200*)
Manufacturer: Degussa
Lot No.: 87A-1 (04169C)
Magnification: 2400×
Voltage: 20 kV



11 Stability and Storage Conditions

Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0–7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system. However, at a pH greater than 7.5 the viscosity-increasing properties of colloidal silicon dioxide are reduced; and at a pH greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates.(13) Colloidal silicon dioxide powder should be stored in a well-closed container.

Some grades of colloidal silicon dioxide have hydrophobic surface treatments that greatly minimize their hygroscopicity.

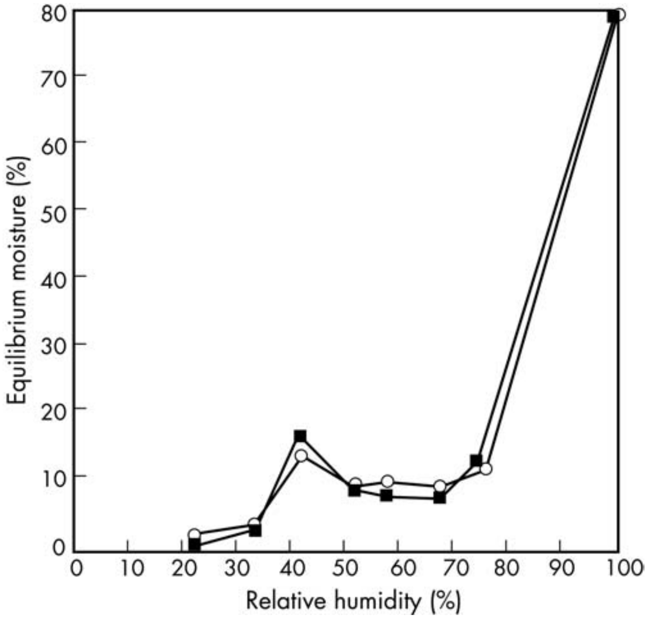


Figure 1: Sorption–desorption isotherm for colloidal silicon dioxide.
○: Sorption
■: Desorption

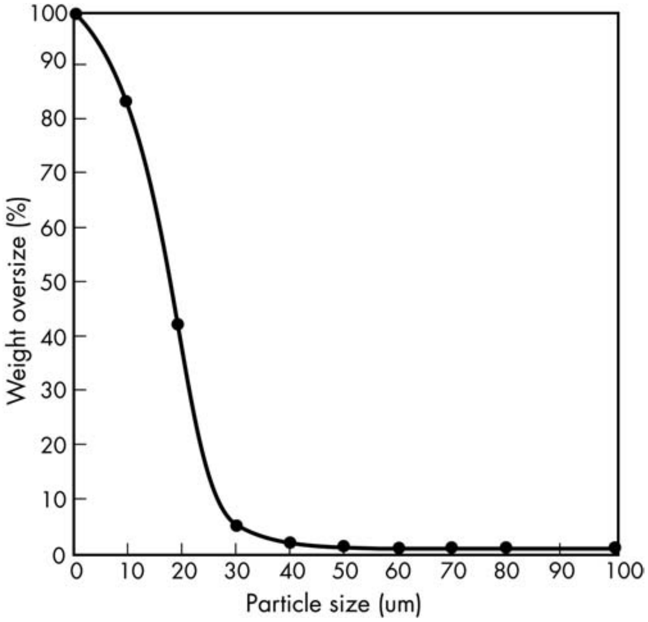


Figure 2: Particle size distribution of colloidal silicon dioxide (*Aerosil A-200*).

12 Incompatibilities

Incompatible with diethylstilbestrol preparations.(15)

13 Method of Manufacture

Colloidal silicon dioxide is prepared by the vapor hydrolysis of chlorosilanes, such as silicon tetrachloride, at 1800°C using a hydrogen–oxygen flame.

14 Safety

Colloidal silicon dioxide is widely used in oral and topical pharmaceutical products and is generally regarded as an essentially nontoxic and nonirritant excipient. However, intraperitoneal and subcutaneous injection may produce local tissue reactions and/or granulomas. Colloidal silicon dioxide should therefore not be administered parenterally.

LD_{50} (rat, IV): 15 mg/kg(16)
LD_{50} (rat, oral): 3.16 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Precautions should be taken to avoid inhalation of colloidal silicon dioxide. In the absence of suitable containment facilities, a dust mask should be worn when handling small quantities of material. For larger quantities, a dust respirator is recommended.

Inhalation of colloidal silicon dioxide dust may cause irritation to the respiratory tract but it is not associated with fibrosis of the lungs (silicosis), which can occur upon exposure to crystalline silica.

16 Regulatory Acceptance

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral capsules, suspensions, and tablets; transdermal and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

—

18 Comments

The PhEur 2005 also contains a specification for hydrated colloidal silicone dioxide. The incidence of microbial contamination of colloidal silicon dioxide is low.

The EINECS number for colloidal silicon dioxide is 231-545-4.

19 Specific References

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21 Authors

SC Owen.

22 Date of Revision

22 August 2005.

Coloring Agents

1 Nonproprietary Names

See Section 17 and Tables I, II, III, and IV.

2 Synonyms

See Section 17 for specific, selected coloring agents.

3 Chemical Name and CAS Registry Number

See Tables I, II, III, and IV.

4 Empirical Formula and Molecular Weight

See Section 17 for specific selected coloring agents.

Table I: European Union list of coloring materials authorized for coloring medicinal products up to January 2002. *See also* Section 16.

E number	Common name	CAS number	Alternate name
E100	Curcumin	[458-37-7]	Turmeric
E101	Riboflavin	[83-88-5]	Lactoflavin
E102	Tartrazine	[1934-21-0]	
E104	Quinoline yellow	[8004-92-0]	
E110	Sunset yellow FCF	[2783-94-0]	
E120	Carmine	[1260-17-9]	Cochineal, carminic acid
E122	Carmoisine	[3567-69-9]	
E123	Amaranth	[915-67-3]	
E124	Ponceau 4R	[2611-82-7]	
E127	Erythrosine	[16423-68-0]	
E129	Allura red AC	[25956-17-6]	
E131	Patent blue V	[3536-49-0]	
E132	Indigo carmine	[860-22-0]	Indigotine
E133	Brilliant blue FCF	[2650-18-2]	
E140	Chlorophylls	[479-61-8] for (i) [519-62-0] for (ii)	Magnesium chlorophyll
E141	Copper complexes of chlorophylls and chlorophyllins	—	
E142	Green S	[3087-16-9]	Brilliant green BS
E150	Caramel	[8028-89-5]	
E151	Brilliant black BN	[2519-30-4]	Black PN
E153	Vegetable carbon	[7440-44-0]	Carbo medicinalis vegetabilis
E160	Carotenoids		
	(a) Alpha-, beta-, gamma-carotene	[7235-40-7]	
	(b) Capsanthin	[465-42-9]	Paprika oleoresin
	(c) Capsorubin	[470-38-2]	Paprika oleoresin
	(d) Lycopene	[502-65-8]	
	(e) Beta-apo-8′ carotenal	[1107-26-2]	
	(f) Ethyl ester of beta-apo-8′ carotenoic acid	—	
E161	Xanthophylls		
	(b) Lutein	[127-40-2]	
	(g) Canthaxanthin	[514-78-3]	
E162	Beetroot red	[7659-95-2]	Betanin
E163	Anthocyanins		
	Cyanidin	[528-58-5]	
	Delphidin	[528-53-0]	
	Malvidin	[643-84-5]	
	Pelargonidin	[134-04-3]	
	Peonidin	[134-01-0]	
	Petunidin	[1429-30-7]	
E170(a)	Calcium carbonate	[471-34-1]	
E171	Titanium dioxide	[13463-67-7]	
E172	Iron oxides and hydroxides	[977053-38-5]	
E173	Aluminum	[7429-90-5]	

(a) For surface coloring only.

Note: List of colors taken from Directive 94/34/EC, Annex I and IV. (*Official Journal EC* 1994; L237/13).

5 Structural Formula

See Section 17 for specific selected coloring agents.

6 Functional Category

Colorants; opacifiers.

7 Applications in Pharmaceutical Formulation or Technology

Coloring agents are used mainly to impart a distinctive appearance to a pharmaceutical dosage form. The main categories of dosage form that are colored are:

- Tablets: either the core itself or the coating.
- Hard or soft gelatin capsules: the capsule shell or coated beads.
- Oral liquids.
- Topical creams and ointments.

Color is a useful tool to help identify a product in its manufacturing and distribution stages. Patients, especially those using multiple products, often rely on color to be able to recognize the prescribed medication.(1) The use of different colors for different strengths of the same drug can also help eliminate errors.

Many drug products look similar; hence color in combination with shape and/or an embossed or printed logo can help with identification. Also, this combination can assist in the prevention of counterfeiting.

Unattractive medication can be made more acceptable to the patient by the use of color, and color can also be used to make a preparation more uniform when an ingredient in the formulation has itself a variable appearance from batch to batch.(2)

Some of the insoluble colors or pigments have the additional benefit when used in tablet coatings or gelatin shells of providing useful opacity, which can contribute to the stability of light-sensitive active materials in the tablet or capsule formulation. Pigments such as the iron oxides, titanium

Table II: Permanently listed color additives subject to US certification in 2002, excluding those approved exclusively for use in medical devices.

Color	Common name	CAS number	21 CFR references to drug use
FD&C blue #1	Brilliant blue FCF	[2650-18-2]	74.1101
FD&C blue #2	Indigotine	[860-22-0]	74.1102
D&C blue #4	Alphazurine FG	[6371-85-3]	74.1104
D&C blue #9	Indanthrene blue	[130-20-1]	74.1109
FD&C green #3	Fast green FCF	[2353-45-9]	74.1203
D&C green #5	Alizarin cyanine green F	[4403-90-1]	74.1205
D&C green #6	Quinizarine green SS	[128-80-3]	74.1206
D&C green #8	Pyranine concentrated	[6358-69-6]	74.1208
D&C orange #4	Orange II	[633-96-5]	74.1254
D&C orange #5	Dibromofluorescein	[596-03-2]	74.1255
D&C orange #10	Diiodofluorescein	[38577-97-8]	74.1260
D&C orange #11	Erythrosine yellowish Na	[38577-97-8]	74.1261
FD&C red #3(a)	Erythrosine	[16423-68-0]	74.1303
FD&C red #4	Ponceau SX	[4548-53-2]	74.1304
D&C red #6	Lithol rubin B	[5858-81-1]	74.1306
D&C red #7	Lithol rubin B Ca	[5281-04-9]	74.1307
D&C red #17	Toney red	[85-86-9]	74.1317
D&C red #21	Tetrabromofluorescein	[15086-94-9]	74.1321
D&C red #22	Eosine	[17372-87-1]	74.1322
D&C red #27	Tetrachlorotetrabromofluorescein	[13473-26-2]	74.1327
D&C red #28	Phloxine B	[18472-87-2]	74.1328
D&C red #30	Helindone pink CN	[2379-74-0]	74.1330
D&C red #31	Brilliant lake red R	[6371-76-2]	74.1331
D&C red #33	Acid fuchsine	[3567-66-6]	74.1333
D&C red #34	Lake bordeaux B	[6417-83-0]	74.1334
D&C red #36	Flaming red	[2814-77-9]	74.1336
D&C red #39	Alba red	[6371-55-7]	74.1339
FD&C red #40	Allura red AC	[25956-17-6]	74.1340
FD&C red #40 lake	Allura Red AC	[68583-95-9]	74.1340
D&C violet #2	Alizurol purple SS	[81-48-1]	74.1602
FD&C yellow #5	Tartrazine	[1934-21-0]	74.1705
FD&C yellow #6	Sunset yellow FCF	[2783-94-0]	74.1706
D&C yellow #7	Fluorescein	[2321-07-5]	74.1707
Ext. D&C yellow #7	Naphthol yellow S	[846-70-8]	74.1707(a)
D&C yellow #8	Uranine	[518-47-8]	74.1708
D&C yellow #10	Quinoline yellow WS	[8004-92-0]	74.1710
D&C yellow #11	Quinoline yellow SS	[8003-22-3]	74.1711

(a) Dye is permanently listed. The lake is not permitted in medicinal products (*see* Table III).

Table III: Provisionally listed color additives subject to US certification in 2002.

Color	Common name	CAS number	21 CFR references to drug use
FD&C lakes	General	*See* individual color	82.51
D&C lakes	General	*See* individual color	82.1051
Ext. D&C lakes	General	*See* individual color	82.2051
FD&C blue #1 lake	Brilliant blue FCF	[53026-57-6]	82.101
FD&C blue #2 lake	Indigotine	[16521-38-3]	82.102
D&C blue #4 lake	Alphazurine FG	[6371-85-3]	82.1104
FD&C green #3 lake	Fast green FCF	[2353-45-9]	82.1203
D&C green #5 lake	Alizarin cyanine green F	[4403-90-1]	82.1205
D&C green #6 lake	Quinizarine green SS	[128-80-3]	82.1206
D&C orange #4 lake	Orange II	[633-56-5]	82.1254
D&C orange #5 lake	Dibromofluorescein	[596-03-2]	74.1255
D&C orange #10 lake	Diiodofluorescein	[38577-97-8]	82.1260
D&C orange #11 lake	Erythosine yellowish Na	[38577-97-8]	82.1261
FD&C red #4 lake	Ponceau SX	[4548-53-2]	82.1304
D&C red #6 lake	Lithol rubin B	[17852-98-1]	82.1306
D&C red #7 lake	Lithol rubin B Ca	[5281-04-9]	82.1307
D&C red #17 lake	Toney red	[85-86-9]	82.1317
D&C red #21 lake	Tetrabromofluorescein	[15086-94-9]	82.1321
D&C red #22 lake	Eosine	[17372-87-1]	82.1322
D&C red #27 lake	Tetrachlorotetrabromo fluorescein	[13473-26-2]	82.1327
D&C red #28 lake	Phloxine B	[18472-87-2]	82.1328
D&C red #30 lake	Helindone pink CN	[2379-74-0]	82.1330
D&C red #31 lake	Brilliant lake red R	[6371-76-2]	82.1331
D&C red #33 lake	Acid fuchsine	[3567-66-6]	82.1333
D&C red #34 lake	Lake bordeaux B	[6417-83-0]	82.1334
D&C red #36 lake	Flaming red	[2814-77-9]	82.1336
D&C violet #2 lake	Alizurol purple SS	[81-48-1]	82.1602
FD&C yellow #5 lake	Tartrazine	[12225-21-7]	82.1705
FD&C yellow #6 lake	Sunset yellow FCF	[15790-07-5]	82.1706
D&C yellow #7 lake	Fluorescein	[2321-07-5]	82.1707
Ext. D&C yellow #7 lake	Naphthol yellow S	[846-70-8]	82.2707
D&C yellow #8 lake	Uranine	[518-47-8]	82.1708
D&C yellow #10 lake	Quinoline yellow WS	[68814-04-0]	82.1710

dioxide, and some of the aluminum lakes are especially useful for this purpose.(3)

Of the many classifications possible for pharmaceutical coloring agents, one of the most useful is to simply divide the colors into those that are soluble in water (dyes) and those that are insoluble in water (pigments).

Colors for clear liquid preparations are limited to the dyes;(4) e.g. *see* Section 17.

For surface coloration, which includes coated tablets, the choice of color is usually restricted to insoluble pigments. The reasons for this include their lack of color migration, greater opacity, and enhanced color stability over water-soluble colors.(5)

Lakes are largely water-insoluble forms of the common synthetic water-soluble dyes. They are prepared by adsorbing a sodium or potassium salt of a dye onto a very fine substrate of hydrated alumina, followed by treatment with a further soluble aluminum salt. The lake is then purified and dried.(6)

Lakes are frequently used in coloring tablet coatings since, for this purpose, they have the general advantages of pigments over water-soluble colors. *See* Table V.

8 Description

The physical appearances of coloring agents vary widely. *See* Section 17 for specific selected coloring agents.

9 Pharmacopeial Specifications

Some materials used as pharmaceutical coloring agents are included in various pharmacopeias; for example, titanium dioxide is included in the PhEur 2005. However, if titanium dioxide is being used exclusively as a colorant, then the specific purity criteria from Directive 95/45/EC apply.(7)

10 Typical Properties

Typical properties of specific selected coloring agents are shown in Section 17. Selected properties are shown in Tables V, VI, and VII.

11 Stability and Storage Conditions

Pharmaceutical coloring agents form a chemically diverse group of materials that have widely varying stability properties. Specific information for selected colors is shown in Table VII and can be found in Woznicki and Schoneker.(4) *See also* Section 17.

While some colors, notably the inorganic pigments, show excellent stability, other coloring agents, such as some organic colors, have poor stability properties but are used in formulations because of their low toxicity.(8)

Table IV: List of color additives exempt from certification permitted for drug use in the USA in 2002.

Color	CAS number	21 CFR references to drug use
Alumina	[1332-73-6]	73.1010
Aluminum powder	[7429-90-5]	73.1645
Annatto extract	[8015-67-6]	73.1030
Beta-carotene	[7235-40-7]	73.1095
Bismuth oxychloride	[7787-59-9]	73.1162
Bronze powder	[7440-66-6]	73.1646
Calcium carbonate	[471-34-1]	73.1070
Canthaxanthin	[514-78-3]	73.1075
Caramel	[8028-89-5]	73.1085
Chromium–cobalt–aluminum oxide	[68187-11-1]	73.1015
Chromium hydroxide green	[12182-82-0]	73.1326
Chromium oxide green	[1308-38-9]	73.1327
Cochineal extract; carmine	[1260-17-9] [1390-65-4]	73.1100
Copper powder	[7440-50-6]	73.1647
Dihydroxyacetone	[62147-49-3]	73.1150
Ferric ammonium citrate	[1185-57-5]	73.1025
Ferric ammonium ferrocyanide	[25869-00-5]	73.1298
Ferric ferrocyanide	[14038-43-8]	73.1299
Guanine	[68-94-0] [73-40-5]	73.1329
Iron oxides synthetic	[977053-38-5]	73.1200
Logwood extract	[8005-33-2]	73.1410
Mica	[12001-26-2]	73.1496
Potassium sodium copper chlorophyllin	—	73.1125
Pyrogallol	[87-66-1]	73.1375
Pyrophyllite	[8047-76-5]	73.1400
Talc	[14807-96-6]	73.1550
Titanium dioxide	[13463-67-7]	73.1575
Zinc oxide	[1314-13-2]	73.1991

Table V: Typical characteristic properties of aluminum lakes.

Average particle size	5–10 μm
Moisture content	12–15%
Oil absorption	40–45(a)
Specific gravity	1.7–2.0 g/cm^3
pH stability range	4.0–8.0

(a) ASTM D281-31, expressed as grams of oil per 100 g of color.

Some natural and synthetic organic colors are particularly unstable in light. However, with appropriate manufacturing procedures, combined with effective product packaging, these colors may be used successfully in formulations, thus making a wide choice of colors practically available.

Lakes, inorganic dyes, and synthetic dyes should be stored in well-closed, light-resistant containers at a temperature below 30°C.

For most natural and nature-identical colors, the storage conditions are more stringent and a manufacturer's recommendations for a particular coloring agent should be followed.

To extend their shelf-life, some natural colors are supplied as gelatin-encapsulated or similarly encapsulated powders and may be sealed in containers under nitrogen.

Table VI: Approximate solubilities for selected colors at 25°C (g/100 mL)(a)

Color	Water	Glycerin	Propylene glycol	Ethanol (95%)	Ethanol (50%)
Brilliant blue FCF	18	20	20	1.5	20
Indigo carmine	1.5	1	0.1	Trace	0.2
FD&C green #3	17	15	15	0.2	7
Erythrosine	12	22	22	2	4
Allura red AC	20	3	1.5	Trace	1
Tartrazine	15	18	8	Trace	4
Sunset yellow	18	15	2	Trace	2

(a) The solubility of individual batches of commercial product will differ widely depending on the amounts of salt, pure dye, moisture and subsidiary dyes present.

12 Incompatibilities

See Section 17 for incompatibilities of specific selected coloring agents; see also Woznicki and Schoneker,(4) and Walford.(9,10)

13 Method of Manufacture

See Section 17 and Walford(9,10) for information on specific selected coloring agents.

14 Safety

Coloring agents are used in a variety of oral and topical pharmaceutical formulations, in addition to their extensive use in foodstuffs and cosmetic products.

Toxicology studies are routinely conducted on an ongoing basis by organizations such as the World Health Organization (WHO), the US Food and Drug Administration (FDA), and the European Commission (EC). The outcome of this continuous review is that the various regulatory bodies around the world have developed lists of permitted colors that are generally regarded as being free from serious adverse toxicological effects. However, owing to the widespread and relatively large use of colors in food, a number of coloring agents in current use have been associated with adverse effects, although in a relatively small number of people.(11,12) Restrictions or bans on the use of some coloring agents have been imposed in some countries, while the same colors may be permitted for use in a different country. As a result the same color may have a different regulatory status in different territories of the world.

The lake of erythrosine (FD&C red #3), for example, has been delisted (*see* Section 16) in the USA since 1990, following studies in rats that suggested that it was carcinogenic. This delisting was as a result of the Delaney Clause, which restricts the use of any color shown to induce cancer in humans or animals in any amount. However, erythrosine was not regarded as being an immediate hazard to health and products containing it were permitted to be used until supplies were exhausted.(13)

Tartrazine (FD&C yellow #5) has also been the subject of controversy over its safety, and restrictions are imposed on its use in some countries; *see* Section 17.

In general, concerns over the safety of coloring agents in pharmaceuticals and foods are associated with reports of hypersensitivity(14–16) and hyperkinetic activity, especially among children.(17)

In the USA, specific labeling requirements are in place for prescription drugs that contain tartrazine (*see* Section 18) as this color was found to be the potential cause of hives in fewer

Table VII: Stability properties of selected colors.

Color	Heat	Light	Acid	Base	Oxidizing agents	Reducing agents
Brilliant blue FCF	Good	Moderate	Very good	Moderate	Moderate	Poor
Indigo carmine	Good	Very poor	Moderate	Poor	Poor	Good
FD&C green #3	Good	Fair	Good	Poor	Poor	Very poor
Erythrosine	Good	Poor	Insoluble	Good	Fair	Very poor
Allura red AC	Good	Moderate	Good	Moderate	Fair	Fair
Tartrazine	Good	Good	Good	Moderate	Fair	Fair
Sunset yellow	Good	Moderate	Good	Moderate	Fair	Fair
D&C yellow #10	Good	Fair	Good	Moderate	Poor	Good

than one in 10 000 people. In the EU, medicinal products containing tartrazine, sunset yellow, carmoisine, amaranth, ponceau 4R or brilliant black BN must carry a warning on the label concerning possible allergic reactions.

15 Handling Precautions

Pharmaceutical coloring agents form a diverse group of materials and manufacturers' data sheets should be consulted for safety and handling data for specific colors.

In general, inorganic pigments and lakes are of low hazard and standard chemical handling precautions should be observed depending upon the circumstances and quantity of material handled. Special care should be taken to prevent excessive dust generation and inhalation of dust.

The organic dyes, natural colors, and nature-identical colors present a greater hazard and appropriate precautions should accordingly be taken.

16 Regulatory Status

Coloring agents have an almost unique status as pharmaceutical excipients in that most regulatory agencies of the world hold positive lists of colors that may be used in medicinal products. Only colors on these lists may be used and some colors may be restricted quantitatively. The legislation also defines purity criteria for the individual coloring agents. In many regions around the world there is a distinction between colors that may be used in drugs and those for food use.

European Union legislation:
The primary legislation that governs coloring matters that may be added to medicinal products is Council Directive 78/25/EEC of 12 December 1977.(18) This Directive links the pharmaceutical requirements with those for foods in the EU. Unfortunately, the Directive makes some specific references to food legislation from 1962 that has subsequently been repealed. However the European Commission has provided guidance on cross references to the current food color legislation as contained in Council Directive 94/36/EC.(19) In addition, the Scientific Committee on Medicinal Products and Medical Devices has delivered opinions on the suitability and safety of amaranth,(20) erythrosine,(21) canthaxanthin,(22) aluminum,(23) and silver(24) as colors for medicines. Silver was considered unsuitable. Table I gives the current position taking the above information into account. Directive 95/45/EC(7) lays down specific purity criteria for food colors and essentially replaces the provisions of the 1962 Directive.

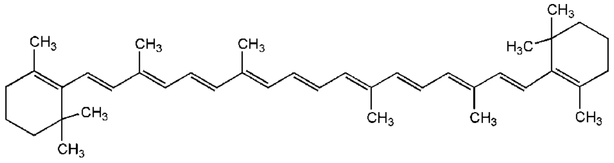
United States legislation:
The 1960 Color Additive Amendment to the Food Drug and Cosmetic Act defines the responsibility of the Food and Drug Administration in the area of pharmaceutical colorants. Tables II, III, and IV provide lists of permitted colors.(25) The list is superficially long, but many of the coloring agents have restricted use. For the so-called certified colors, the FDA operates a scheme whereby each batch of color produced is certified as analytically correct by the FDA prior to the issuing of a certification number and document that will permit sale of the batch in question. Colors requiring certification are described as FD&C (Food Drug and Cosmetic); D&C (Drug and Cosmetic) or External D&C. The remaining colors are described as uncertified colors and are mainly of natural origin. The USA also operates a system of division of certified colors into permanently and provisionally listed colors. Provisionally listed colors require the regular intervention of the FDA Commissioner to provide continued listing of these colors. Should the need arise, the legislative process for removal of these colors from use is comparatively easy.

Licensing authority approval:
In addition to national approvals and lists, a pharmaceutical licensing authority can impose additional restrictions at the time of application review. Within the EU this generally takes the form of restricting colors, such as tartrazine and other azo colors, in medicinal products for chronic administration, and especially in medicines for allergic conditions.

17 Related Substances

Beta-carotene; indigo carmine; iron oxides; sunset yellow FCF; tartrazine; titanium dioxide.

Beta-carotene
Empirical formula: $C_{40}H_{56}$
Molecular weight: 536.85
CAS number: [7235-40-7]
Synonyms: betacarotene; β-carotene; β,β-carotene; E160a.
Structure:



Appearance: occurs in the pure state as red crystals when recrystallized from light petroleum.

Color Index No.:
CI 75130 (natural)
CI 40800 (synthetic)
Melting point: 183°C
Purity (EU):
Arsenic: $\leqslant$3 ppm
Lead: $\leqslant$10 ppm
Mercury: $\leqslant$1 ppm
Cadmium: $\leqslant$1 ppm
Heavy metals: $\leqslant$40 ppm
Assay: $\geqslant$96% total coloring matters expressed as beta-carotene
Identification: maximum in cyclohexane at 453–456 nm
Sulfated ash: $\leqslant$0.2%
Subsidiary coloring matters: carotenoids other than beta-carotene, $\leqslant$3.0% of total coloring matters.
Purity (US):
Arsenic: $\leqslant$3 ppm
Assay: 96–101%
Lead: $\leqslant$10 ppm
Residue on ignition: $\leqslant$0.2%
Loss on drying: $\leqslant$0.2%

Solubility: soluble 1 in 30 parts of chloroform; practically insoluble in ethanol, glycerin, and water.

Incompatibilities: generally incompatible with oxidizing agents; decolorization will take place.

Stability: beta-carotene is very susceptible to oxidation and antioxidants such as ascorbic acid, sodium ascorbate, or tocopherols should be added. Store protected from light at a low temperature (–20°C) in containers sealed under nitrogen.

Method of manufacture: all industrial processes for preparing carotenoids are based on β-ionone. This material can be obtained by total synthesis from acetone and acetylene via dehydrolinalol. The commercially available material is usually 'extended' on a matrix such as acacia or maltodextrin. These extended forms of beta-carotene are dispersible in aqueous systems. Beta-carotene is also available as micronized crystals suspended in an edible oil such as peanut oil.

Comments: beta-carotene is capable of producing colors varying from pale yellow to dark orange. It can be used as a color for sugar-coated tablets prepared by the ladle process. However, beta-carotene is very unstable to light and air, and products containing this material should be securely packaged to minimize degradation. Beta-carotene is particularly unstable when used in spray-coating processes, probably owing to atmospheric oxygen attacking the finely dispersed spray droplets.

Because of its poor water solubility, beta-carotene cannot be used to color clear aqueous systems, and cosolvents such as ethanol must be used.

Suppositories have been successfully colored with beta-carotene in approximately 0.1% concentration.

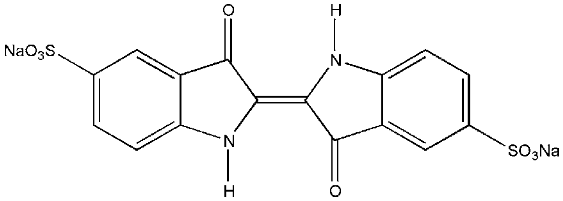
The EINECS number for beta-carotene is 230-636-6.

Indigo carmine

Empirical formula: $C_{16}H_8N_2Na_2O_8S_2$
Molecular weight: 466.37
CAS number: [860-22-0]

Synonyms: 2-(1,3-dihydro-3-oxo-5-sulfo-2*H*-indol-2-ylidene)-2,3-dihydro-3-oxo-1*H*-indole-5-sulfonic acid disodium salt; disodium 5,5′-indigotin disulfonate; E132; FD&C blue #2; indigotine; sodium indigotin disulfonate; soluble indigo blue.

Structure:



Appearance: dark blue powder. Aqueous solutions are blue or bluish-purple.
Absorption maximum: 604 nm
Color Index No.: CI 73015
Purity (EU):
Arsenic: $\leqslant$3 ppm
Lead: $\leqslant$10 ppm
Mercury: $\leqslant$1 ppm
Cadmium: $\leqslant$1 ppm
Heavy metals: $\leqslant$40 ppm
Ether-extractable matter: $\leqslant$0.2% under neutral conditions
Accessory colorings: $\leqslant$1.0%
Isatin-5-sulfonic acid: $\leqslant$1.0%
Water-insoluble matter: $\leqslant$0.2%
Assay: $\geqslant$85% total coloring matters, calculated as the sodium salt
Disodium 3,3′-dioxo-2,2′-biindoylidene-5,7′-disulfonate: $\leqslant$18%.
Water-insoluble matter: $\leqslant$0.2%.
Subsidiary coloring matters: excluding provision above, $\leqslant$1.0%
Organic compounds other than coloring matters: $\leqslant$0.5%
Unsulfonated primary aromatic amines: $\leqslant$0.01%, as aniline
Purity (US):
Arsenic: $\leqslant$3 ppm
2-(1,3-Dihydro-3-oxo-2*H*-indol-2-ylidene)-2,3-dihydro-3-oxo-1*H*-indole-5-sulfonic acid sodium salt: $\leqslant$2%
2-(1,3-Dihydro-3-oxo-7-sulfo-2*H*-indol-2-ylidene)-2,3-dihydro-3-oxo-1*H*-indole-5-sulfonic acid disodium salt: $\leqslant$18%
Isatin-5-sulfonic acid: $\leqslant$0.4%
Lead: $\leqslant$10 ppm
Mercury: $\leqslant$1 ppm
5-Sulfoanthranilic acid: $\leqslant$0.2%
Total color: $\geqslant$85%
Volatile matter, chlorides and sulfates (calculated as the sodium salts): $\leqslant$15.0% at 135°C
Water-insoluble matter: $\leqslant$0.4%
Solubility: *see* Table VIII.

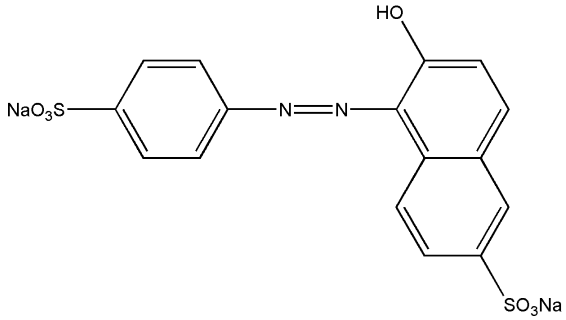
Table VIII: Solubility of indigo carmine.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	Practically insoluble
Ethanol (75%)	1 in 1430
Glycerin	1 in 100
Propylene glycol	1 in 1000
Propylene glycol (50%)	1 in 167
Water	1 in 125 at 2°C 1 in 63 at 25°C 1 in 45 at 60°C

Incompatibilities: poorly compatible with citric acid and saccharose solutions. Incompatible with ascorbic acid, gelatin, glucose, lactose, oxidizing agents, and saturated sodium bicarbonate solution.
Stability: sensitive to light.
Method of manufacture: indigo is sulfonated with concentrated or fuming sulfuric acid.
Safety: LD_{50} (rat, IV): 93 mg/kg
Comments: Indigo carmine is an indigoid dye used to color oral and topical pharmaceutical preparations. It is used with yellow colors to produce green colors. Indigo carmine is also used to color nylon surgical sutures and is used diagnostically as a 0.8% w/v injection.

Sunset yellow FCF

Empirical formula: $C_{16}H_{10}N_2Na_2O_7S_2$
Molecular weight: 452.37
CAS number: [2783-94-0]
Synonyms: E110; FD&C yellow #6; 6-hydroxy-5-[(4-sulfophenyl)azo]-2-naphthalenesulfonic acid disodium salt; 1-*p*-sulfophenylazo-2-naphthol-6-sulfonic acid disodium salt; yellow orange S.
Structure:



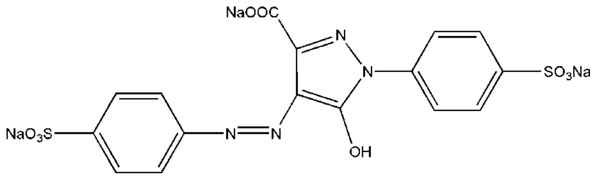
Appearance: reddish yellow powder. Aqueous solutions are bright orange colored.
Absorption maximum: 482 nm
Color Index No.: CI 15985
Purity (EU):
Arsenic: ⩽3 ppm
Lead: ⩽10 ppm
Mercury: ⩽1 ppm
Cadmium: ⩽1 ppm
Heavy metals: ⩽40 ppm
Ether-extractable matter: ⩽0.2% under neutral conditions
Assay: ⩾85% total coloring matters as the sodium salt
Subsidiary colors: ⩽5%
Water-insoluble matter: ⩽0.2%
Organic compounds other than coloring matters: ⩽0.5%
Unsulfonated primary aromatic amines: ⩽0.01% as aniline
Ether-extractable matter: ⩽0.2% under neutral conditions
Purity (US):
Arsenic: ⩽3 ppm
Lead: ⩽10 ppm
Mercury: ⩽1 ppm
4-Aminobenzenesulfonic acid: ⩽0.2% as the sodium salt
6-Hydroxy-2-naphthalenesulfonic acid: ⩽0.3% as the sodium salt
6,6′-Oxybis[2-naphthalenesulfonic acid]: ⩽1% as the disodium salt
4,4′-(1-Triazene-1,3-diyl)bis[benzenesulfonic acid]: ⩽0.1% as the disodium salt
4-Aminobenzene: ⩽50 ppb
4-Aminobiphenyl: ⩽15 ppb
Aniline: ⩽250 ppb
Azobenzene: ⩽200 ppb
Benzidine: ⩽1 ppb
1,3-Diphenyltriazene: ⩽40 ppb
1-(Phenylazo)-2-naphthalenol: ⩽10 ppm
Total color: ⩾87%
Sum of volatile matter at 135°C, chlorides and sulfates: ⩽13.0%
Water-insoluble matter: ⩽0.2%
Solubility: *see* Table IX.
Incompatibilities: poorly compatible with citric acid, saccharose solutions, and saturated sodium bicarbonate solutions. Incompatible with ascorbic acid, gelatin, and glucose.
Method of manufacture: diazotized sulfanilic acid is coupled with Schaeffer's salt (sodium salt of β-naphthol-6-sulfonic acid).
Safety:
LD_{50} (mouse, IP): 4.6 g/kg
LD_{50} (mouse, oral): >6 g/kg
LD_{50} (rat, IP): 3.8 g/kg
LD_{50} (rat, oral): >10 g/kg
Comments: sunset yellow FCF is a monoazo dye.
The EINECS number for sunset yellow FCF is 220-491-7.

Table IX: Solubility of Sunset yellow FCF.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	1 in 38.5
Ethanol (75%)	1 in 333
Glycerin	1 in 5
Propylene glycol	1 in 45.5
Propylene glycol (50%)	1 in 5
Water	1 in 5.3 at 2°C
	1 in 5.3 at 25°C
	1 in 5 at 60°C

Tartrazine

Empirical formula: $C_{16}H_9N_4Na_3O_9S_2$
Molecular weight: 534.39
CAS number: [1934-21-0]
Synonyms: 4,5-dihydro-5-oxo-1-(4-sulfophenyl)-4-[(4-sulfophenyl)azo]-1*H*-pyrazole-3-carboxylic acid trisodium salt; E102; FD&C yellow #5; hydrazine yellow.
Structure:



Appearance: yellow or orange-yellow powder. Aqueous solutions are yellow-colored; the color is retained upon addition of hydrochloric acid solution, but with sodium hydroxide solution a reddish color is formed.
Absorption maximum: 425 nm
Color Index No.: CI 19140
Purity (EU):
Arsenic: ⩽3 ppm
Lead: ⩽10 ppm

Mercury: ⩽1 ppm
Cadmium: ⩽1 ppm
Heavy metals: ⩽40 ppm
Assay: ⩾85% total coloring matters as the sodium salt
Organic compounds other than coloring matters: ⩽0.5%
Unsulfonated primary aromatic amines: ⩽0.01% as aniline
Ether-extractable matter: ⩽0.2% under neutral conditions
Accessory colorings: ⩽1.0%
Water-insoluble matter: ⩽0.2%

Purity (US):
Arsenic: ⩽3 ppm
Lead: ⩽10 ppm
Mercury: ⩽1 ppm
Total color: ⩾87.0%
Volatile matter, chlorides and sulfates (calculated as the sodium salts): ⩽13.0% at 135°C
Water-insoluble matter: ⩽0.2%
4,4′-[4,5-Dihydro-5-oxo-4-[(4-sulfophenyl)hydrazono]-1*H*-pyrazol-1,3-diyl]bis[benzenesulfonic acid]: ⩽0.1% as the trisodium salt
4-Aminobenzenesulfonic acid: ⩽0.2% as the sodium salt
4,5-Dihydro-5-oxo-1-(4-sulfophenyl)-1*H*-pyrazole-3-carboxylic acid: ⩽0.2% as the disodium salt
Ethyl or methyl 4,5-dihydro-5-oxo-1-(4-sulfophenyl)-1*H*-pyrazole-3-carboxylate: ⩽0.1% as the sodium salt
4,4′-(1-Triazene-1,3-diyl)bis[benzenesulfonic acid]: ⩽0.05% as the disodium salt
4-Aminobenzene: ⩽75 ppb
4-Aminobiphenyl: ⩽5 ppb
Aniline: ⩽100 ppb
Azobenzene: ⩽40 ppb
Benzidine: ⩽1 ppb
1,3-Diphenyltriazene: ⩽40 ppb

Solubility: *see* Table X.

Table X: Solubility of tartrazine.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	Practically insoluble
Ethanol (75%)	1 in 91
Glycerin	1 in 5.6
Propylene glycol	1 in 14.3
Propylene glycol (50%)	1 in 5
Water	1 in 26 at 2°C
	1 in 5 at 25°C
	1 in 5 at 60°C

Incompatibilities: poorly compatible with citric acid solutions. Incompatible with ascorbic acid, lactose, 10% glucose solution, and saturated aqueous sodium bicarbonate solution. Gelatin accelerates the fading of the color.

Method of manufacture: phenylhydrazine *p*-sulfonic acid is condensed with sodium ethyl oxalacetate; the product obtained from this reaction is then coupled with diazotized sulfanilic acid.

Safety:
LD_{50} (mouse, oral): >6 g/kg
LD_{50} (mouse, IP): 4.6 g/kg
LD_{50} (rat, oral): 10 g/kg
LD_{50} (rat, IP): 3.8 g/kg

Comments: tartrazine is a monoazo, or pyrazolone, dye. It is used to improve the appearance of a product and to impart a distinctive coloring for identification purposes.

US regulations require that prescription drugs for human use containing tartrazine bear the warning statement:

> This product contains FD&C yellow #5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons.

Although the overall incidence of sensitivity to FD&C yellow #5 (tartrazine) in the general population is low, it is frequently seen in patients who are also hypersensitive to aspirin.

18 Comments

Titanium dioxide is used extensively to impart a white color to film-coated tablets, sugar-coated tablets, and gelatin capsules. It is also used in lakes as an opacifier, to 'extend' the color. *See* Titanium dioxide for further information.

In the EU, colors used in pharmaceutical formulations and colors used in cosmetics are controlled by separate regulations. Cosmetic colors are also classified according to their use, e.g. those that may be used in external products that are washed off after use.

19 Specific References

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20 General References

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21 Authors

C Mroz.

22 Date of Revision

27 August 2005.

Copovidone

1 Nonproprietary Names

BP: Copovidone
PhEur: Copovidonum
USPNF: Copovidone

2 Synonyms

Acetic acid vinyl ester, polymer with 1-vinyl-2-pyrrolidinone; copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate in a ratio of 3 : 2 by mass; copolyvidone; *Kollidon VA 64*; *Luviskol VA*; *Plasdone S-630*; poly(1-vinylpyrrolidone–co-vinyl acetate); polyvinylpyrrolidone–vinyl acetate copolymer; PVP/VA; PVP/VA copolymer.

3 Chemical Name and CAS Registry Number

Acetic acid ethenyl ester, polymer with 1-ethenyl-2-pyrrolidinone [25086-89-9]

4 Empirical Formula and Molecular Weight

$(C_6H_9NO)_n \cdot (C_4H_6O_2)_m$ $(111.1)n + (86.1)m$

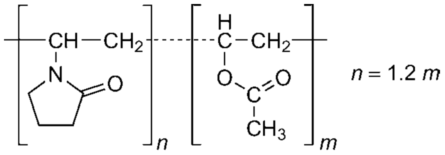
The ratio of n to m is approximately $n = 1.2m$. Molecular weights of 45 000–70 000 have been determined for *Kollidon VA 64*. The average molecular weight of copovidone is usually expressed as a K-value.

The K-value of *Kollidon VA 64* is nominally 28, with a range of 25.2–30.8. The K-value of *Plasdone S 630* is specified between 25.4 and 34.2. K-values are calculated from the kinematic viscosity of a 1% aqueous solution. Molecular weight can be calculated with the formula:

$M = 22.22\ (K + 0.075K^2)^{1.65}$

The PhEur 2005 and USPNF 23 (Suppl. 1) describe copovidone as a copolymer of 1-ethenylpyrrolidin-2-one and ethenyl acetate in the mass proportion of 3 : 2.

5 Structural Formula



6 Functional Category

Film-former; granulating agent; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Copovidone is used as a tablet binder, a film-former, and as part of the matrix material used in controlled-release formulations. In tableting, copovidone can be used as a binder for direct compression(1–3) and as a binder in wet granulation.(4,5) Copovidone is often added to coating solutions as a film-forming agent. It provides good adhesion, elasticity, and hardness, and can be used as a moisture barrier.

See Table I.

Table I: Uses of copovidone.

Use	Concentration (%)
Film-forming agent	0.5–5.0[a]
Tablet binder, direct compression	2.0–5.0
Tablet binder, wet granulation	2.0–5.0

[a] This corresponds to the % w/w copovidone in the film-forming solution formulation, before spraying.

8 Description

Copovidone is a white to yellowish-white amorphous powder. It is typically spray-dried with a relatively fine particle size. It has a slight odor and a faint taste.

9 Pharmacopeial Specifications

See Table II.

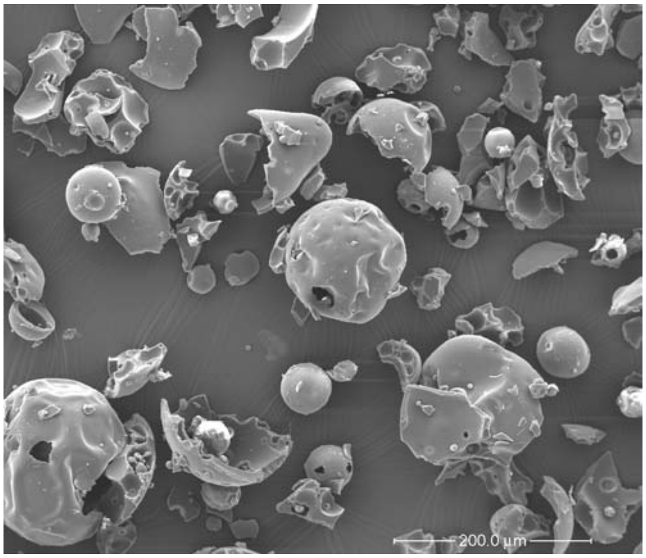
Table II: Pharmacopeial specifications for copovidone.

Test	PhEur 2005	USPNF 23 (Suppl. 1)
Aldehydes	⩽500 ppm	⩽0.05%
Appearance of solution	+	+
Characters	+	—
Ethenyl acetate	35.3–42.0%	35.3–41.4%
Heavy metals	⩽20 ppm	—
Hydrazine	⩽1 ppm	⩽1 ppm
Identification	+	+
K-value	90–110%	90.0–110.0%
Loss on drying	⩽5.0%	⩽5.0%
Monomers	⩽0.1%	⩽0.1%
Nitrogen content	7.0–8.0%	7.0–8.0%
Peroxides	⩽400 ppm	⩽0.04%
2-Pyrrolidone	⩽0.5%	—
Sulfated ash	⩽0.1%	⩽0.1%
Viscosity, expressed as *K*-value	+	—

10 Typical Properties

Density(bulk): 0.24–0.28 g/cm^3
Density (tapped): 0.35–0.45 g/cm^3
Flash point: 215°C
Flowability: relatively free-flowing powder.
Glass transition temperature: 106°C for *Plasdone S-630*.(6)
Hygroscopicity: at 50% relative humidity, copovidone gains less than 10% weight.
K-value: 25.4–34.2 for *Plasdone S-630*.(6)

SEM: 1
Excipient: Copovidone (*Kollidon VA 64*)
Manufacturer: BASF
Magnification: 400×
Voltage: 10 kV



Melting point: 140°C

Solubility: greater than 10% solubility in 1,4-butanediol, glycerol, butanol, chloroform, dichloromethane, ethanol (95%), glycerol, methanol, polyethylene glycol 400, propan-2-ol, propanol, propylene glycol, and water. Less than 1% solubility in cyclohexane, diethyl ether, liquid paraffin, and pentane.

Viscosity (dynamic): the viscosity of aqueous solutions depends on the molecular weight and the concentration. At concentrations less than 10%, the viscosity is less than 10 mPa s (25°C).

11 Stability and Storage Conditions

Copovidone is stable and should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Copovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to high water levels, copovidone may form molecular adducts with some materials; see Crospovidone and Povidone.

13 Method of Manufacture

Copovidone is manufactured by free-radical polymerization of vinylpyrrolidone and vinyl acetate in a ratio of 6 : 4. The synthesis is conducted in an organic solvent owing to the insolubility of vinyl acetate in water.

14 Safety

Copovidone is used widely in pharmaceutical formulations and is generally regarded as nontoxic. However, it is moderately toxic by ingestion, producing gastric disturbances. It has no irritating or sensitizing effects on the skin.

LD_{50} (rat, oral): >0.63 g/kg(7)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. When heated to decomposition, copovidone emits toxic vapors of NO_x. Eye protection, gloves, and a dust mask are recommended.

16 Regulatory Status

Copovidone is included in the FDA Inactive Ingredients Guide (oral tablets, oral film-coated tablets, sustained action).

17 Related Substances

Crospovidone; povidone.

18 Comments

Kollidon VA 64, has a spherical structure, with a high proportion of damaged spheres. The shell-like structure reduces flowability, but the damaged spheres cover a greater surface area of the filler particles, increasing the efficacy of its use as a dry binder.(8) Furthermore, when used in transdermal drug delivery systems, copovidone has been shown to significantly alter the melting behavior, by reducing the heat of fusion and the melting point of estradiol and various other sex steroids.(9)

Plasdone S-630 has been used in direct compression experiments with active substances that are difficult to compress, such as acetaminophen (paracetamol); and has been shown to produce harder tablets than those containing the same actives but made with microcrystalline cellulose.(10)

In general, copovidone has better plasticity than povidone as a tablet binder, and is less hygroscopic, more elastic, and less tacky in film-forming applications than povidone.

Up to about 1975, copovidone was marketed by BASF under the name *Luviskol VA 64*. *Luviskol* is currently used only for the technical/cosmetic grade of copovidone.

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21 Authors

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22 Date of Revision

1 August 2005.

Corn Oil

1 Nonproprietary Names

BP: Refined maize oil
JP: Corn oil
PhEur: Maydis oleum raffinatum
USPNF: Corn oil

2 Synonyms

Maize oil; *Majsao CT.*

3 Chemical Name and CAS Registry Number

Corn oil [8001-30-7]

4 Empirical Formula and Molecular Weight

Corn oil is composed of fatty acid esters with glycerol, known commonly as triglycerides. Typical corn oil produced in the USA contains five major fatty acids: linoleic 58.9%; oleic 25.8%; palmitic 11.0%; stearic 1.7%; and linolenic 1.1%. Corn grown outside the USA yields corn oil with lower linoleic, higher oleic, and higher saturated fatty acid levels. Corn oil also contains small quantities of plant sterols.

The USPNF 23 describes corn oil as the refined fixed oil obtained from the embryo of *Zea mays* Linné (Fam. Gramineae).

5 Structural Formula

See Section 4.

6 Functional Category

Oleaginous vehicle; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Corn oil is used primarily in pharmaceutical formulations as a solvent for intramuscular injections or as a vehicle for topical preparations. Emulsions containing up to 67% corn oil are also used as oral nutritional supplements; *see also* Section 18. When combined with surfactants and gel-forming polymers, it is used to formulate veterinary vaccines.

Corn oil has a long history of use as an edible oil and may be used in tablets or capsules for oral administration.

8 Description

Clear, light yellow-colored, oily liquid with a faint characteristic odor and slightly nutty, sweet taste resembling cooked sweet corn.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for corn oil.

Test	JP 2001	PhEur 2005	USPNF 23
Acid value	≤0.2	≤0.5	—
Alkaline impurities	—	+	—
Characters	+	+	—
Cottonseed oil	—	—	+
Composition of fatty acids	—	+	+
Fatty acids less than C_{16}	—	≤0.6%	—
Arachidic acid	—	≤0.8%	—
Behenic acid	—	≤0.5%	—
Oleic acid	—	20.0–42.2%	—
Eicosaenoic acid	—	≤0.5%	—
Linoleic acid	—	39.4–65.6%	—
Linolenic acid	—	0.5–1.5%	—
Palmitic acid	—	8.6–16.5%	—
Stearic acid	—	≤3.3%	—
Other fatty acids	—	≤0.5%	—
Sterols	—	≤0.3%	—
Water	—	≤0.1%	—
Free fatty acids	—	—	+
Heavy metals	—	—	≤0.001%
Iodine value	103–130	—	102–130
Organic volatile impurities	—	—	+
Peroxide value	—	≤10.0	—
Refractive index	—	1.474	—
Saponification value	187–195	—	187–193
Specific gravity	0.915–0.921	0.920	0.914–0.921
Unsaponifiable matter	≤1.5%	≤2.8%	≤1.5%

10 Typical Properties

Acid value: 2–6
Autoignition temperature: 393°C
Density: 0.915–0.918 g/cm^3
Flash point: 321°C
Hydroxyl value: 8–12
Melting point: -18 to -10°C
Refractive index:
n_D^{25} = 1.470–1.474;
n_D^{40} = 1.464–1.468.
Solubility: miscible with benzene, chloroform, dichloromethane, ether, and hexane; practically insoluble in ethanol (95%) and water.
Viscosity (dynamic): 37–39 mPa s (37–39 cP)

11 Stability and Storage Conditions

Corn oil is stable when protected with nitrogen in tightly sealed bottles. Prolonged exposure to air leads to thickening and rancidity. Corn oil may be sterilized by dry heat, maintaining it at 150°C for 1 hour.(1)

Corn oil should be stored in an airtight, light-resistant container in a cool, dry place. Exposure to excessive heat should be avoided.

12 Incompatibilities

The photooxidation of corn oil is sensitized by cosmetic and drug-grade samples of coated titanium oxide and zinc oxide.(2)

13 Method of Manufacture

Refined corn oil is obtained from the germ or embryo of *Zea mays* Linné (Fam. Gramineae), which contains nearly 50% of the fixed oil compared with 3.0–6.5% in the whole kernel. The oil is obtained from the embryo by expression and/or solvent extraction. Refining involves the removal of free fatty acids, phospholipids, and impurities; decolorizing with solid adsorbents; dewaxing by chilling; and deodorization at high temperature and under vacuum.

14 Safety

Corn oil is generally regarded as a relatively nontoxic and nonirritant material with an extensive history of usage in food preparation.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Spillages of this material are very slippery and should be covered with an inert absorbent material prior to disposal.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IM injections, oral capsules and tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Almond oil; canola oil; cottonseed oil; peanut oil; sesame oil; soybean oil; sunflower oil.

18 Comments

Owing to its high content of unsaturated acids, corn oil has been used as a replacement for fats and oils containing a high content of saturated acids in the diets of patients with hypercholesterolemia.

A specification for corn oil is contained in the Food Chemicals Codex (FCC). The EINECS number for corn oil is 232-281-2.

19 Specific References

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21 Authors

KS Alexander

22 Date of Revision

22 August 2005.

Cottonseed Oil

1 Nonproprietary Names

USPNF: Cottonseed oil

2 Synonyms

Cotton oil; refined cottonseed oil.

3 Chemical Name and CAS Registry Number

Cottonseed oil [8001-29-4]

4 Empirical Formula and Molecular Weight

A typical analysis of refined cottonseed oil indicates the composition of the acids present as glycerides to be as follows: linoleic acid 39.3%; oleic acid 33.1%; palmitic acid 19.1%; stearic acid 1.9%; arachidic acid 0.6%, and myristic acid 0.3%. Also present are small quantities of phospholipid, phytosterols, and pigments. The toxic polyphenolic pigment gossypol is present in raw cottonseed and in the oil cake remaining after expression of oil; it is not found in the refined oil.

5 Structural Formula

See Section 4.

6 Functional Category

Oleaginous vehicle; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Cottonseed oil is used in pharmaceutical formulations primarily as a solvent for intramuscular injections. It has been used in intravenous emulsions as a fat source in parenteral nutrition regimens, although its use for this purpose has been superseded by soybean oil emulsions; *see* Section 14. It has also been used as an adjuvant in cholecystography and as a pediculicide and acaricide. It has the nutritive and emollient properties of fixed vegetable oils. By virtue of its high content of unsaturated acid glycerides (especially linoleic acid), it is used for dietary control of blood cholesterol levels in the prophylaxis and treatment of atherosclerosis. It is used as a solvent and vehicle for injections; as an emollient vehicle for other medications; and orally as a mild cathartic (in a dose of 30 mL or more). It can also retard gastric secretion and motility, and increase caloric intake. It has been used in the manufacture of soaps, oleomargarine, lard substitutes, glycerin, lubricants, and cosmetics.

Cottonseed oil has been used as a tablet binder for acetaminophen; for characterization of the hot-melt fluid bed coating process;(1) in the manufacturing of stable oral pharmaceutical powders; in encapsulation of enzymes; and as an aqueous dispersion in pharmaceutical coating.

8 Description

Pale yellow or bright golden yellow-colored, clear oily liquid. It is odorless, or nearly so, with a bland, nutty taste. At temperatures below 10°C particles of solid fat may separate from the oil, and at about –5 to 0°C the oil becomes solid or nearly so. If it solidifies, the oil should be remelted and thoroughly mixed before use.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for cottonseed oil.

Test	USPNF 23
Identification	+
Free fatty acids	+
Heavy metals	$\leqslant$0.001%
Iodine value	109–120
Organic volatile impurities	+
Specific gravity	0.915–0.921

10 Typical Properties

Autoignition temperature: 344°C
Density: 0.916 g/cm^3
Flash point: 321°C
Freezing point: -5 to 0°C
Heat of combustion: 37.1 kJ/g
Refractive index: n_D^{40} = 1.4645–1.4655
Solubility: slightly soluble in ethanol (95%); miscible with carbon disulfide, chloroform, ether, hexane, and petroleum ether.
Surface tension:
35.4 mN/m (35.4 dynes/cm) at 20°C;
31.3 mN/m (31.3 dynes/cm) at 80°C.
Viscosity (dynamic): up to 70.4 mPa s (70.4 cP) at 20°C

11 Stability and Storage Conditions

Cottonseed oil is stable if stored in a well-filled, airtight, light-resistant container in a cool, dry place.

12 Incompatibilities

—

13 Method of Manufacture

Cottonseed oil is the refined fixed oil obtained from the seed of cultivated varieties of *Gossypium hirsutum* Linné or of other species of *Gossypium* (Fam. Malvaceae). The seeds contain about 15% oil. The testae of the seeds are first separated and the kernels are then exposed to powerful expression in a hydraulic press. The crude oil thus obtained has a bright red or blackish-red color and requires purification before it is suitable for food or pharmaceutical purposes.

Cottonseed oil is refined by treatment with diluted alkali to neutralize acids, decolorized with fuller's earth or activated carbon, deodorized with steam under reduced pressure, and chilled to separate glycerides and resinous substances of higher melting point.

14 Safety

Cottonseed oil emulsions have in the past been used in long-term intravenous nutrition regimens.(2,3) A complex of adverse reactions, called the 'overloading syndrome'(4) has been seen with chronic administration of cottonseed oil emulsion. This consisted of anorexia, nausea, abdominal pain, headache, fever, and sore throat. Signs of impaired liver function, anemia, hepatosplenomegaly, thrombocytopenia, and spontaneous hemorrhage due to delayed blood clotting have been reported. For parenteral nutrition purposes, cottonseed oil has been replaced by soybean oil,(2,5,6) especially in pregnant women, where the use of cottonseed lipid emulsion has been associated with adverse effects.(7)

A notable difference between the cottonseed oil emulsion and the soybean oil emulsion is the particle size. The cottonseed oil emulsion has much larger particles than the soybean oil emulsion. These larger particles may have been handled differently by the body, thus perhaps accounting for some of the toxic reactions.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Spillages of this material are very slippery and should be covered with an inert absorbent material prior to disposal.

Cottonseed oil is a combustible liquid when exposed to heat or flame. If it is allowed to impregnate rags or oily waste, there is a risk due to spontaneous heating. Dry chemicals such as carbon dioxide should be used to fight any fires.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IM injections, oral, capsule, tablet and sublingual preparations). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Almond oil; canola oil; corn oil; hydrogenated vegetable oil; peanut oil; sesame oil; soybean oil; sunflower oil.

18 Comments

A specification for unhydrogenated cottonseed oil is contained in the Food Chemicals Codex (FCC). The EINECS number for cottonseed oil is 232-280-7.

19 Specific References

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20 General References

—

21 Authors

KS Alexander.

22 Date of Revision

22 August 2005.

Cresol

1 Nonproprietary Names

BP: Cresol
JP: Cresol
USPNF: Cresol

2 Synonyms

Cresylic acid; cresylol; hydroxytoluene; tricresol.

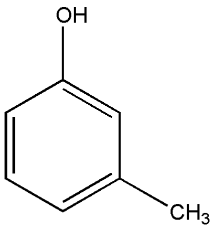
3 Chemical Name and CAS Registry Number

Methylphenol [1319-77-3]

4 Empirical Formula and Molecular Weight

C_7H_8O 108.14

5 Structural Formula



m-Cresol

6 Functional Category

Antimicrobial preservative; disinfectant.

7 Applications in Pharmaceutical Formulation or Technology

Cresol is used at 0.15–0.3% concentration as an antimicrobial preservative in intramuscular, intradermal, and subcutaneous injectable pharmaceutical formulations. It is also used as a preservative in some topical formulations and as a disinfectant. Cresol is not suitable as a preservative for preparations that are to be freeze-dried.(1)

8 Description

Cresol consists of a mixture of cresol isomers, predominantly *m*-cresol, and other phenols obtained from coal tar or petroleum. It is a colorless, yellowish to pale brownish-yellow, or pink-colored liquid, with a characteristic odor similar to phenol but more tarlike. An aqueous solution has a pungent taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for cresol.

Test	BP 2004	JP 2001	USPNF 23
Identification	+	+	+
Characters	+	—	—
Specific gravity	1.029–1.044	1.032–1.041	1.030–1.038
Distilling range	+	+	195–205°C
Acidity	+	—	—
Hydrocarbons	⩽0.15%	+	+
Volatile bases	⩽0.15%	—	—
Hydrocarbons and volatile bases combined	⩽0.25%	—	—
Phenol	—	—	⩽5.0%
Sulfur compounds	+	+	—
Nonvolatile matter	⩽0.1%	—	—

10 Typical Properties

Acidity/alkalinity: a saturated aqueous solution is neutral or slightly acidic to litmus.

Antimicrobial activity: cresol is similar to phenol but has slightly more antimicrobial activity. It is moderately active against Gram-positive bacteria, less active against Gram-negative bacteria, yeasts, and molds. Cresol is active below pH 9; optimum activity is obtained in acidic conditions. Synergistic effects between cresol and other preservatives have been reported.(2,3) When used as a disinfectant most common pathogens are killed within 10 minutes by 0.3–0.6% solutions. Cresol has no significant activity against bacterial spores.

Solubility: *see* Table II.

Table II: Solubility of cresol.

Solvent	Solubility at 20°C
Benzene	Miscible
Chloroform	Freely soluble
Ethanol (95%)	Freely soluble
Ether	Freely soluble
Fixed alkali hydroxides	Freely soluble
Fixed and volatile oils	Freely soluble
Glycerin	Miscible
Water	1 in 50

11 Stability and Storage Conditions

Cresol and aqueous cresol solutions darken in color with age and on exposure to air and light.

Cresol should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

Cresol has been reported to be incompatible with chlorpromazine.(4) Antimicrobial activity is reduced in the presence of nonionic surfactants.

13 Method of Manufacture

Cresol may be obtained from coal tar or prepared synthetically by either sulfonation or oxidation of toluene.

14 Safety

Reports of adverse reactions to cresol are generally associated with the use of either the bulk material or cresol-based disinfectants, which may contain up to 50% cresol, rather than for its use as a preservative.

Cresol is similar to phenol although it is less caustic and toxic. However, cresol is sufficiently caustic to be unsuitable for skin and wound disinfection. In studies in rabbits, cresol was found to be metabolized and excreted primarily as the glucuronide.(5)

A patient has survived ingestion of 12 g of cresol though with severe adverse effects.(6)

LD_{50} (mouse, oral): 0.76 g/kg(7)
LD_{50} (rabbit, skin): 2 g/kg
LD_{50} (rat, oral): 1.45 g/kg

See also Sections 17 and 18.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Cresol may be irritant to the skin, eyes, and mucous membranes. Eye protection, gloves, and a respirator are recommended. In the UK, the occupational exposure limit for cresol is 22 mg/m^3 (5 ppm) long-term (8-hour TWA).(8) In the USA, the permissible and recommended exposure limits are 22 mg/m^3 long-term and 10 mg/m^3 long-term respectively.(9)

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IM, IV, intradermal, and SC injections). Included in parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Chlorocresol; *m*-cresol; *o*-cresol; *p*-cresol; phenol.

m-Cresol

Empirical formula: C_7H_8O
Molecular weight: 108.14
CAS number: [108-39-4]
Synonyms: *m*-cresylic acid; 3-hydroxytoluene; *meta*-cresol; 3-methylphenol.
Appearance: colorless or yellowish liquid with a characteristic phenolic odor.
Boiling point: 202°C
Density: 1.034 g/cm^3 at 20°C
Flash point: 86°C (closed cup)
Melting point: 11–12°C
Refractive index: $n_D^{20} = 1.5398$
Solubility: soluble in organic solvents; soluble 1 in 40 parts of water.
Safety:

LD_{50} (cat, SC): 0.15 g/kg(7,10)
LD_{50} (mouse, IP): 0.17 g/kg
LD_{50} (mouse, oral): 0.83 g/kg
LD_{50} (mouse, SC): 0.45 g/kg
LD_{50} (rabbit, IV): 0.28 g/kg
LD_{50} (rabbit, oral): 1.1 g/kg
LD_{50} (rabbit, SC): 0.5 g/kg
LD_{50} (rabbit, skin): 2.05 g/kg
LD_{50} (rat, oral): 2.02 g/kg
LD_{50} (rat, skin): 1.1 g/kg

o-Cresol

Empirical formula: C_7H_8O
Molecular weight: 108.14
CAS number: [95-48-7]
Synonyms: *o*-cresylic acid; 2-hydroxytoluene; 2-methylphenol; *ortho*-cresol.
Appearance: colorless deliquescent solid with a characteristic odor; it becomes yellow on storage.
Boiling point: 191–192°C
Density: 1.047 g/cm^3 at 20°C
Flash point: 81–83°C (closed cup)
Melting point: 30°C
Refractive index: $n_D^{20} = 1.553$
Safety:

LD_{50} (cat, SC): 0.6 g/kg(7,10)
LD_{50} (mouse, oral): 0.34 g/kg
LD_{50} (mouse, SC): 0.35 g/kg
LD_{50} (mouse, skin): 0.62 g/kg
LD_{50} (rabbit, IV): 0.2 g/kg
LD_{50} (rabbit, oral): 0.8 g/kg
LD_{50} (rabbit, SC): 0.45 g/kg
LD_{50} (rat, oral): 1.35 g/kg
LD_{50} (rat, skin): 0.62 g/kg

p-Cresol

Empirical formula: C_7H_8O
Molecular weight: 108.14
CAS number: [106-44-5]
Synonyms: *p*-cresylic acid; 4-hydroxytoluene; 4-methylphenol; *para*-cresol.
Appearance: crystalline solid.
Boiling point: 201.8°C
Density: 1.0341 g/cm^3 at 20°C
Flash point: 86°C (closed cup)
Melting point: 35.5°C
Refractive index: $n_D^{20} = 1.5395$
Solubility: soluble in ethanol (95%) and ether; very slightly soluble in water.
Safety:

LD_{50} (cat, SC): 0.08 g/kg(7,10)
LD_{50} (mouse, IP): 0.03 g/kg
LD_{50} (mouse, oral): 0.34 g/kg
LD_{50} (mouse, SC): 0.15 g/kg
LD_{50} (rabbit, IV): 0.16 g/kg
LD_{50} (rabbit, oral): 1.1 g/kg
LD_{50} (rabbit, SC): 0.3 g/kg
LD_{50} (rabbit, skin): 0.3 g/kg
LD_{50} (rat, oral): 1.80 g/kg
LD_{50} (rat, skin): 0.75 g/kg

18 Comments

m-Cresol is generally considered the least toxic of the three cresol isomers.(10) Inhalation of aerosolized *m*-cresol in pulmonary insulin delivery formulations has been shown to be safe in animal models.(11)

The PhEur 2005 contains a specification for cresol, crude.

The EINECS number for cresol is 203–577–9.

19 Specific References

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6 Côté MA, Lyonnais J, Leblond PF. Acute Heinz-body anemia due to severe cresol poisoning: successful treatment with erythrocytapheresis. *Can Med Assoc J* 1984; **130**: 1319–1322.

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21 Authors

LY Galichet.

22 Date of Revision

17 August 2005.

Croscarmellose Sodium

1 Nonproprietary Names

BP: Croscarmellose sodium
PhEur: Carmellosum natricum conexum
USPNF: Croscarmellose sodium

2 Synonyms

Ac-Di-Sol; crosslinked carboxymethylcellulose sodium; *Explocel*; modified cellulose gum; *Nymcel ZSX*; *Pharmacel XL*; *Primellose*; *Solutab*; *Vivasol*.

3 Chemical Name and CAS Registry Number

Cellulose, carboxymethyl ether, sodium salt, crosslinked [74811-65-7]

4 Empirical Formula and Molecular Weight

Croscarmellose sodium is a crosslinked polymer of carboxymethylcellulose sodium.

See Carboxymethylcellulose sodium.

5 Structural Formula

See Carboxymethylcellulose sodium.

6 Functional Category

Tablet and capsule disintegrant.

7 Applications in Pharmaceutical Formulation or Technology

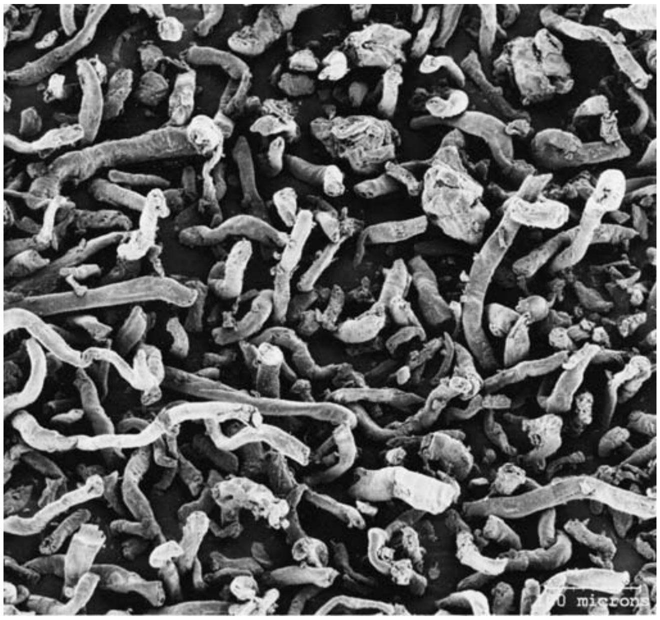
Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules,(1,2) tablets,(3–13) and granules.

In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized.(11,12) Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process. *See* Table I.

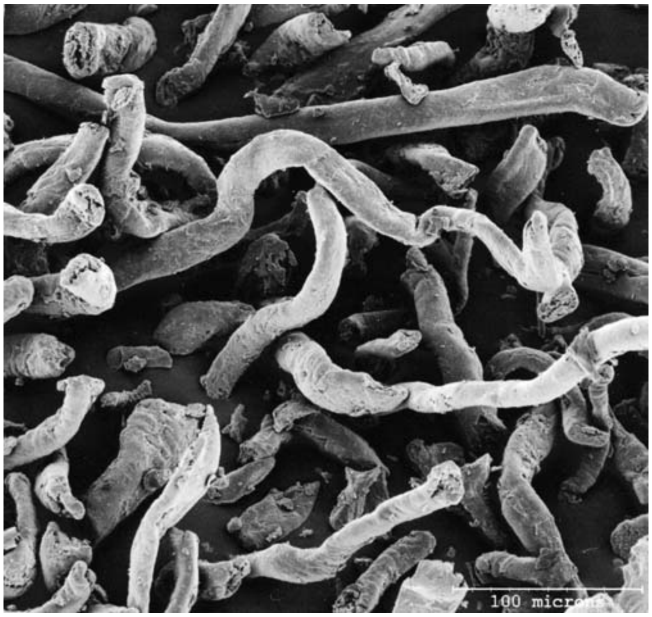
Table I: Uses of croscarmellose sodium.

Use	Concentration (%)
Disintegrant in capsules	10–25
Disintegrant in tablets	0.5–5.0

SEM: 1
Excipient: Croscarmellose sodium (*Ac-Di-Sol*)
Manufacturer: FMC Biopolymer
Magnification: 100×



SEM: 2
Excipient: Croscarmellose sodium (*Ac-Di-Sol*)
Manufacturer: FMC Biopolymer
Magnification: 1000×



8 Description

Croscarmellose sodium occurs as an odorless, white or grayish-white powder.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for croscarmellose sodium.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
pH (1% w/v dispersion)	5.0–7.0	5.0–7.0
Loss on drying	⩽10.0%	⩽10.0%
Heavy metals	⩽10 ppm	⩽0.001%
Sodium chloride and sodium glycolate	⩽0.5%	⩽0.5%
Sulfated ash	14.0–28.0%	—
Degree of substitution	0.60–0.85	0.60–0.85
Content of water-soluble material	⩽10.0%	1.0–10.0%
Settling volume	10.0–30.0 ml	10.0–30.0 ml
Microbial contamination	+	—
Aerobic	10^3/g	10^3/g
Fungi	10^2/g	10^2/g
Organic volatile impurities	—	+

10 Typical Properties

Acidity/alkalinity: pH = 5.0–7.0 in aqueous dispersions.
Bonding index: 0.0456
Brittle fracture index: 0.1000
Density (bulk): 0.529 g/cm^3 for *Ac-Di-Sol*(7)
Density (tapped): 0.819 g/cm^3 for *Ac-Di-Sol*(7)
Density (true): 1.543 g/cm^3 for *Ac-Di-Sol*(7)
Particle size distribution:

Ac-Di-Sol: not more than 2% retained on a #200 (73.7 μm) mesh and not more than 10% retained on a #325 (44.5 μm) mesh.

Pharmacel XL: more than 90% less than 45 μm, and more than 98% less than 100 μm in size.

Solubility: insoluble in water, although croscarmellose sodium rapidly swells to 4–8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.
Specific surface area: 0.81–0.83 m^2/g

11 Stability and Storage Conditions

Croscarmellose sodium is a stable though hygroscopic material.

A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 30°C for 14 months.(9)

Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol.(10)

Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

13 Method of Manufacture

Alkali cellulose is prepared by steeping cellulose, obtained from wood pulp or cotton fibers, in sodium hydroxide solution. The alkali cellulose is then reacted with sodium monochloroacetate to obtain carboxymethylcellulose sodium. After the substitution reaction is completed and all of the sodium hydroxide has been used, the excess sodium monochloroacetate slowly hydrolyzes to glycolic acid. The glycolic acid changes a few of the sodium carboxymethyl groups to the free acid and catalyzes the formation of crosslinks to produce croscarmellose sodium. The croscarmellose sodium is then extracted with aqueous alcohol and any remaining sodium chloride or sodium glycolate is removed. After purification, croscarmellose sodium of purity greater than 99.5% is obtained.(4) The croscarmellose sodium may be milled to break the polymer fibers into shorter lengths and hence improve its flow properties.

14 Safety

Croscarmellose sodium is mainly used as a disintegrant in oral pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material. However, oral consumption of large amounts of croscarmellose sodium may have a laxative effect, although the quantities used in solid dosage formulations are unlikely to cause such problems.

In the UK, croscarmellose sodium is accepted for use in dietary supplements.

The WHO has not specified an acceptable daily intake for the related substance carboxymethylcellulose sodium, used as a food additive, since the levels necessary to achieve a desired effect were not considered sufficient to be a hazard to health.(14)

See also Carboxymethylcellulose sodium.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Croscarmellose sodium may be irritant to the eyes; eye protection is recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules, granules, sublingual tablets, and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Carboxymethylcellulose calcium; carboxymethylcellulose sodium.

18 Comments

Typically, the degree of substitution (DS) for croscarmellose sodium is 0.7.

19 Specific References

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21 Authors

RT Guest.

22 Date of Revision

23 August 2005.

Crospovidone

1 Nonproprietary Names

BP: Crospovidone
PhEur: Crospovidonum
USPNF: Crospovidone

2 Synonyms

Crosslinked povidone; E1202; *Kollidon CL*; *Kollidon CL-M*; *Polyplasdone XL*; *Polyplasdone XL-10*; polyvinylpolypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer.

3 Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4 Empirical Formula and Molecular Weight

$(C_6H_9NO)_n$ >1 000 000

The USPNF 23 describes crospovidone as a water-insoluble synthetic crosslinked homopolymer of *N*-vinyl-2-pyrrolidinone. An exact determination of the molecular weight has not been established because of the insolubility of the material.

5 Structural Formula

See Povidone.

6 Functional Category

Tablet disintegrant.

7 Applications in Pharmaceutical Formulation or Technology

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods.(1–6) It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets.(7) Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

8 Description

Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for crospovidone.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
pH (1% suspension)	—	5.0–8.0
Water	—	⩽5.0%
Residue on ignition	⩽0.1%	⩽0.4%
Water-soluble substances	⩽1.0%	⩽1.50%
Peroxides	⩽400 ppm	—
Heavy metals	⩽10 ppm	⩽0.001%
Vinylpyrrolidinone	—	⩽0.1%
Loss on drying	⩽5.0%	—
Nitrogen content (anhydrous basis)	11.0–12.8%	+

10 Typical Properties

Acidity/alkalinity: pH = 5.0–8.0 (1% w/v aqueous slurry)
Density: 1.22 g/cm^3
Density (bulk): *see* Table II.
Density (tapped): *see* Table II.

Table II: Density values of commercial grades of crospovidone.

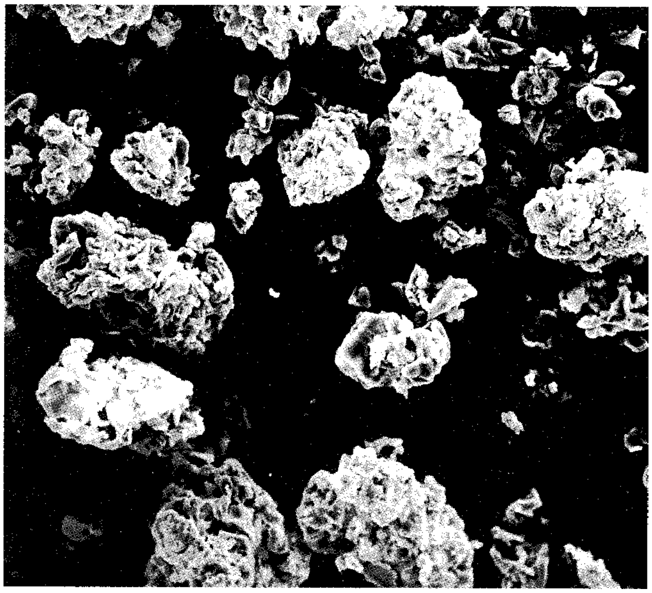
Commercial grade	Density (bulk) g/cm^3	Density (tapped) g/cm^3
Kollidon CL	0.3–0.4	0.4–0.5
Kollidon CL-M	0.15–0.25	0.3–0.5
Polyplasdone XL	0.213	0.273
Polyplasdone XL-10	0.323	0.461

Moisture content: maximum moisture sorption is approximately 60%.
Particle size distribution: less than 400 μm for *Polyplasdone XL*; less than 74 μm for *Polyplasdone XL-10*. Approximately 50% greater than 50 μm and maximum of 3% greater than 250 μm in size for *Kollidon CL*. Minimum of 90% of particles are below 15 μm for *Kollidon CL-M*.
Solubility: practically insoluble in water and most common organic solvents.
Specific surface area: *see* Table III.

Table III: Specific surface areas for commercial grades of crospovidone.

Commercial grade	Surface area (m^2/g)
Kollidon CL	1.0
Kollidon CL-M	3.0–6.0
Polyplasdone XL	0.6–0.8
Polyplasdone XL-10	1.2–1.4

SEM 1
Excipient: Crospovidone (*Polyplasdone XL-10*)
Manufacturer: ISP Corp.
Lot No.: S81031
Magnification: 400×
Voltage: 10 kV



11 Stability and Storage Conditions

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials; *see* Povidone.

13 Method of Manufacture

Acetylene and formaldehyde are reacted in the presence of a highly active catalyst to form butynediol, which is hydrogenated to butanediol and then cyclodehydrogenated to form butyrolactone. Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reaction in which pyrrolidone and acetylene are reacted under pressure. The monomer vinylpyrrolidone is then polymerized in solution, using a catalyst. Crospovidone is prepared by a 'popcorn polymerization' process.

14 Safety

Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. Short-term animal toxicity studies have shown no adverse effects associated with crospovidone.(8) However, owing to the lack of available data, an acceptable daily intake in humans has not been specified by the WHO.(8)

LD_{50} (mouse, IP): 12 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

16 Regulatory Status

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IM injections, oral capsules and tablets; topical, transdermal, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Copovidone; povidone.

18 Comments

Crospovidone has been studied as a superdisintegrant. The ability of the compound to swell has been examined directly using scanning electron microscopy.(9) The impact of crospovidone on percolation has also been examined.(10) The impact of crospovidone on dissolution of poorly soluble drugs in tablets has also been investigated.(11)

A specification for crospovidone is contained in the Food Chemicals Codex (FCC).

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21 Authors

AH Kibbe.

22 Date of Revision

25 August 2005.

Cyclodextrins

1 Nonproprietary Names

BP: Betadex
PhEur: Betadexum
USPNF: Betadex
Note: β-cyclodextrin (betadex) is the only cyclodextrin to be currently described in a pharmacopeia. Alfadex is the rINN for α-cyclodextrin.

2 Synonyms

Cyclodextrin: *Cavitron*; cyclic oligosaccharide; cycloamylose; cycloglucan; *Encapsin*; Schardinger dextrin.
α-Cyclodextrin: alfadex; alpha-cycloamylose; alpha-cyclodextrin; alpha-dextrin; *Cavamax W6 Pharma*; cyclohexaamylose; cyclomaltohexose.
β-Cyclodextrin: beta-cycloamylose; beta-dextrin; *Cavamax W7 Pharma*; cycloheptaamylose; cycloheptaglucan; cyclomaltoheptose; *Kleptose*.
γ-Cyclodextrin: *Cavamax W8 Pharma*; cyclooctaamylose; gamma cyclodextrin.

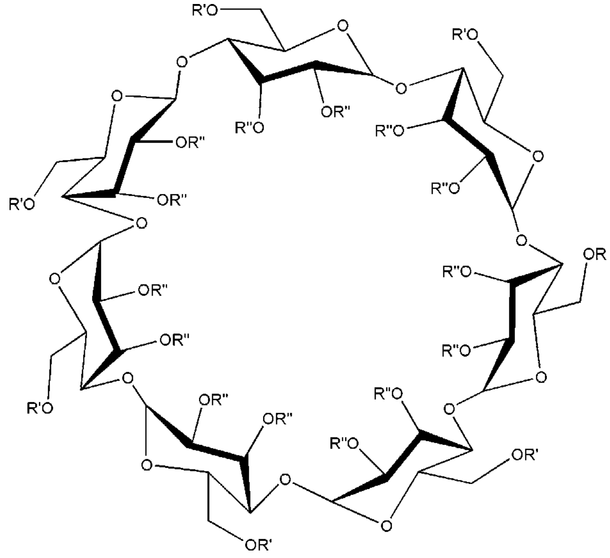
3 Chemical Name and CAS Registry Number

α-Cyclodextrin	[10016-20-3]
β-Cyclodextrin	[7585-39-9]
γ-Cyclodextrin	[17465-86-0]

4 Empirical Formula and Molecular Weight

α-Cyclodextrin	$C_{36}H_{60}O_{30}$	972
β-Cyclodextrin	$C_{42}H_{70}O_{35}$	1135
γ-Cyclodextrin	$C_{48}H_{80}O_{40}$	1297

5 Structural Formula



Note: the structure of β-cyclodextrin (7 glucose units) is shown.

R′, R″ = H for ‘natural’ α-, β- and γ-cyclodextrins
R′, R″ = CH_3 for methyl cyclodextrins
R′, R″ = $CHOHCH_3$ for 2-hydroxyethyl cyclodextrins
R′, R″ = $CH_2CHOHCH_3$ for 2-hydroxypropyl cyclodextrins

6 Functional Category

Solubilizing agent; stabilizing agent.

7 Applications in Pharmaceutical Formulation or Technology

Cyclodextrins are crystalline, nonhygroscopic, cyclic oligosaccharides derived from starch. Among the most commonly used forms are α-, β-, and γ-cyclodextrin, which have respectively 6, 7, and 8 glucose units; *see* Section 5.

Substituted cyclodextrin derivatives are also available; *see* Section 17.

Cyclodextrins are ‘bucketlike’ or ‘conelike’ toroid molecules, with a rigid structure and a central cavity, the size of which varies according to the cyclodextrin type; *see* Section 8. The internal surface of the cavity is hydrophobic and the outside of the torus is hydrophilic; this is due to the arrangement of hydroxyl groups within the molecule. This arrangement permits the cyclodextrin to accommodate a guest molecule within the cavity, forming an inclusion complex.

Cyclodextrins may be used to form inclusion complexes with a variety of drug molecules, resulting primarily in improvements to dissolution and bioavailability owing to enhanced solubility and improved chemical and physical stability; *see* Section 18.

Cyclodextrin inclusion complexes have also been used to mask the unpleasant taste of active materials and to convert a liquid substance into a solid material.

β-Cyclodextrin is the most commonly used cyclodextrin, although it is the least soluble; *see* Section 10. It is the least expensive cyclodextrin; is commercially available from a number of sources; and is able to form inclusion complexes with a number of molecules of pharmaceutical interest. However, β-cyclodextrin is nephrotoxic and should not be used in parenteral formulations; *see* Section 14.

β-Cyclodextrin is considered to be nontoxic when administered orally, and is primarily used in tablet and capsule formulations. β-Cyclodextrin derivatives tend to be nontoxic when used either orally or parenterally, and the derivatives 2-hydroxypropyl-β-cyclodextrin and 3-hydroxypropyl-β-cyclodextrin are becoming increasingly important in pharmaceutical formulations.(1–5)

α-Cyclodextrin is used mainly in parenteral formulations. However, as it has the smallest cavity of the cyclodextrins it can form inclusion complexes with only relatively few, small-sized molecules. In contrast, γ-cyclodextrin has the largest cavity and can be used to form inclusion complexes with large molecules; it has low toxicity and enhanced water solubility.

In oral tablet formulations, β-cyclodextrin may be used in both wet-granulation and direct-compression processes. The physical properties of β-cyclodextrin vary depending on the manufacturer. However, β-cyclodextrin tends to possess poor flow properties and requires a lubricant, such as 0.1% w/w magnesium stearate, when it is directly compressed.(6,7)

In parenteral formulations, cyclodextrins have been used to produce stable and soluble preparations of drugs that would otherwise have been formulated using a nonaqueous solvent.

In eye drop formulations, cyclodextrins form water-soluble complexes with lipophilic drugs such as corticosteroids. They have been shown to increase the water solubility of the drug; to enhance drug absorption into the eye; to improve aqueous stability; and to reduce local irritation.(8)

Cyclodextrins have also been used in the formulation of solutions,(9,10) suppositories,(11,12) and cosmetics.(13,14)

8 Description

Cyclodextrins are cyclic oligosaccharides containing at least six D-(+)-glucopyranose units attached by α(1→4) glucoside bonds. The three natural cyclodextrins, α, β, and γ, differ in their ring size and solubility. They contain 6, 7, or 8 glucose units, respectively.

Cyclodextrins occur as white, practically odorless, fine crystalline powders, having a slightly sweet taste. Some cyclodextrin derivatives occur as amorphous powders.

The PhEur 2005 lists α-cyclodextrin and γ-cyclodextrin as potential impurities in β-cyclodextrin.

See also Table I.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for β-cyclodextrin (betadex).

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Color and clarity of solution	+	+
pH	5.0–8.0	—
Specific rotation	+160 to +164°	+160 to +164°
Microbial limits	—	⩽1000/g[a]
Sulfated ash	⩽0.1%	⩽0.1%
Heavy metals	⩽10 ppm	⩽5 ppm
Light-absorbing impurities	+	—
Loss on drying	⩽16.0%	⩽14.0%
Related substances	+	—
Residual solvents	+	—
Reducing sugars	⩽0.2%	⩽1.0%
Assay (anhydrous basis)	98.0–101.0%	98.0–101.0%

[a] Tests for *Salmonella* and *Escherichia coli* are negative.

10 Typical Properties

Compressibility: 21.0–44.0% for β-cyclodextrin.
Density (bulk):
α-cyclodextrin: 0.526 g/cm^3;
β-cyclodextrin: 0.523 g/cm^3;
γ-cyclodextrin: 0.568 g/cm^3.
Density (tapped):
α-cyclodextrin: 0.685 g/cm^3;
β-cyclodextrin: 0.754 g/cm^3;
γ-cyclodextrin: 0.684 g/cm^3.
Density (true):
α-cyclodextrin: 1.521 g/cm^3;
γ-cyclodextrin: 1.471 g/cm^3.
Melting point:
α-cyclodextrin: 250–260°C;
β-cyclodextrin: 255–265°C;
γ-cyclodextrin: 240–245°C.
Moisture content:
α-cyclodextrin: 10.2% w/w;
β-cyclodextrin: 13.0–15.0% w/w;
γ-cyclodextrin: 8–18% w/w.
Particle size distribution:
β-cyclodextrin: 7.0–45.0 μm
Physical characteristics: *see* Table II.

Table II: Physical characteristics of cyclodextrins.

Characteristic	Cyclodextrin		
	α	β	γ
Cavity diameter (A)	4.7–5.3	6.0–6.5	7.5–8.3
Height of torus (A)	7.9	7.9	7.9
Diameter of periphery (A)	14.6	15.4	17.5
Approximate volume of cavity (A^3)	174	262	472
Approximate cavity volume			
Per mol cyclodextrin (mL)	104	157	256
Per g cyclodextrin (mL)	0.1	0.14	0.20

Note: 1 A = 0.1 nm.

Solubility:
α-cyclodextrin: soluble 1 in 7 parts of water at 20°C, 1 in 3 at 50°C.
β-cyclodextrin: soluble 1 in 200 parts of propylene glycol, 1 in 50 of water at 20°C, 1 in 20 at 50°C; practically insoluble in acetone, ethanol (95%), and methylene chloride.
γ-cyclodextrin: soluble 1 in 4.4 parts of water at 20°C, 1 in 2 at 45°C.
Specific rotation $[\alpha]_D^{25}$:
α-cyclodextrin: +150.5°;
β-cyclodextrin: +162.0°;
γ-cyclodextrin: +177.4°.
Surface tension (at 25°C):
α-cyclodextrin: 71 mN/m (71 dynes/cm);
β-cyclodextrin: 71 mN/m (71 dynes/cm);
γ-cyclodextrin: 71 mN/m (71 dynes/cm).

11 Stability and Storage Conditions

β-Cyclodextrin and other cyclodextrins are stable in the solid state if protected from high humidity.

Cyclodextrins should be stored in a tightly sealed container, in a cool, dry place.

12 Incompatibilities

The activity of some antimicrobial preservatives in aqueous solution can be reduced in the presence of hydroxypropyl-β-cyclodextrin.(15–17)

13 Method of Manufacture

Cyclodextrins are manufactured by the enzymatic degradation of starch using specialized bacteria. For example, β-cyclodextrin is produced by the action of the enzyme cyclodextrin glucosyltransferase upon starch or a starch hydrolysate. An organic solvent is used to direct the reaction that produces β-cyclodextrin, and to prevent the growth of microorganisms during the enzymatic reaction. The insoluble complex of β-cyclodextrin and organic solvent is separated from the noncyclic starch, and the organic solvent is removed *in vacuo* so that less than 1 ppm of solvent remains in the β-cyclodextrin. The β-cyclodextrin is then carbon treated and crystallized from water, dried, and collected.

Hydroxyethyl-β-cyclodextrin is made by reacting β-cyclodextrin with ethylene oxide; hydroxypropyl-β-cyclodextrin is made by reacting β-cyclodextrin with propylene oxide.

14 Safety

Cyclodextrins are starch derivatives and are mainly used in oral and parenteral pharmaceutical formulations. They are also used in topical and ophthalmic formulations.(8)

Cyclodextrins are also used in cosmetics and food products, and are generally regarded as essentially nontoxic and nonirritant materials. However, when administered parenterally, β-cyclodextrin is not metabolized but accumulates in the kidneys as insoluble cholesterol complexes, resulting in severe nephrotoxicity.(18) Other cyclodextrins, such as 2-hydroxypropyl-β-cyclodextrin, have been the subject of extensive toxicological studies. They are not associated with nephrotoxicity and are reported to be safe for use in parenteral formulations.(3)

Cyclodextrin administered orally is metabolized by microflora in the colon, forming the metabolites maltodextrin, maltose, and glucose; which are themselves further metabolized before being finally excreted as carbon dioxide and water. Although a study published in 1957 suggested that orally administered cyclodextrins were highly toxic,(19) more recent animal toxicity studies in rats and dogs have shown this not to be the case, and cyclodextrins are now approved for use in food products and orally administered pharmaceuticals in a number of countries.

Cyclodextrins are not irritant to the skin and eyes, or upon inhalation. There is also no evidence to suggest that cyclodextrins are mutagenic or teratogenic.

α-Cyclodextrin:
- LD_{50} (rat, IP): 1.0 g/kg(20)
- LD_{50} (rat, IV): 0.79 g/kg

β-Cyclodextrin:
- LD_{50} (mouse, IP): 0.33 g/kg(21)
- LD_{50} (mouse, SC): 0.41 g/kg
- LD_{50} (rat, IP): 0.36 g/kg
- LD_{50} (rat, IV): 1.0 g/kg
- LD_{50} (rat, oral): 18.8 g/kg
- LD_{50} (rat, SC): 3.7 g/kg

γ-Cyclodextrin:
- LD_{50} (rat, IP): 4.6 g/kg(20)
- LD_{50} (rat ,IV): 4.0 g/kg
- LD_{50} (rat, oral): 8.0 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Cyclodextrins are fine organic powders and should be handled in a well-ventilated environment. Efforts should be made to limit the generation of dust, which can be explosive.

16 Regulatory Status

β-cyclodextrin is included in the FDA Inactive Ingredients guide (IM, IV injections, and other injection preparations).

Included in the Canadian List of Acceptable Non-medicinal Ingredients (stabilizing agent; solubilizing agent); and in oral and rectal pharmaceutical formulations licensed in Europe, Japan, and the USA.

17 Related Substances

Dimethyl-β-cyclodextrin; 2-hydroxyethyl-β-cyclodextrin; 2-hydroxypropyl-β-cyclodextrin; 3-hydroxypropyl-β-cyclodextrin; trimethyl-β-cyclodextrin.

Dimethyl-β-cyclodextrin

Molecular weight: 1331
Synonyms: DM-β-CD.
Appearance: white crystalline powder.
Cavity diameter: 6 Å
Melting point: 295.0–300.0°C
Moisture content: ⩽1% w/w
Solubility: soluble 1 in 135 parts of ethanol (95%), and 1 in 1.75 of water at 25°C. Solubility decreases with increasing temperature.
Surface tension: 62 mN/m (62 dynes/cm) at 25°C
Method of manufacture: dimethyl-β-cyclodextrin is prepared from β-cyclodextrin by the selective methylation of all C2 secondary hydroxyl groups and all C6 primary hydroxyl groups (C3 secondary hydroxyl groups remain unsubstituted).
Comments: used in applications similar to those for β-cyclodextrin.(2,3)

2-Hydroxyethyl-β-cyclodextrin

CAS number: [98513-20-3]
Synonyms: 2-HE-β-CD.
Appearance: white crystalline powder.
Density (bulk): 0.681 g/cm^3
Density (tapped): 0.916 g/cm^3
Density (true): 1.378 g/cm^3
Solubility: greater than 1 in 2 parts of water at 25°C.
Surface tension: 68.0–71.0 mN/m (68–71 dynes/cm) at 25°C.
Comments: used in applications similar to those for β-cyclodextrin. The degree of substitution of hydroxyethyl groups can vary.(2,3,22)

2-Hydroxypropyl-β-cyclodextrin

CAS number: [128446-35-5]
Synonyms: 2-HP-β-CD; *Kleptose HPB*.
Appearance: white crystalline powder.
Solubility: greater than 1 in 2 parts of water at 25°C.
Surface tension: 52.0–69.0 mN/m (52–69 dynes/cm) at 25°C.
Comments: used in applications similar to those for β-cyclodextrin. However, as it is not nephrotoxic it has been suggested for use in parenteral formulations. Included in oral and parenteral pharmaceutical formulations licensed in Europe and the USA. The degree of substitution of hydroxypropyl groups can vary.(1–5)

3-Hydroxypropyl-β-cyclodextrin

Synonyms: 3-HP-β-CD.
Appearance: white crystalline powder.
Solubility: greater than 1 in 2 parts of water at 25°C.
Surface tension: 70.0–71.0 mN/m (70–71 dynes/cm) at 25°C.

Comments: used in applications similar to those for β-cyclodextrin. However, as it is not nephrotoxic it has been suggested for use in parenteral formulations. The degree of substitution of hydroxypropyl groups can vary.(2,3)

Trimethyl-β-cyclodextrin
Molecular weight: 1429
Synonyms: TM-β-CD.
Appearance: white crystalline powder.
Cavity diameter: 4.0–7.0 Å
Melting point: 157°C
Moisture content: ⩽1% w/w
Solubility: soluble 1 in 3.2 parts of water at 25°C. Solubility decreases with increasing temperature.
Surface tension: 56 mN/m (56 dynes/cm) at 25°C.
Method of manufacture: trimethyl-β-cyclodextrin is prepared from β-cyclodextrin by the complete methylation of all C2 and C3 secondary hydroxyl groups along with all C6 primary hydroxyl groups.
Comments: used in applications similar to those for β-cyclodextrin.(2,3)

18 Comments

In addition to their use in pharmaceutical formulations, cyclodextrins have also been investigated for use in various industrial applications. Analytically, cyclodextrin polymers are used in chromatographic separations, particularly of chiral materials.

β-Cyclodextrin derivatives are more water-soluble than β-cyclodextrin, and studies have shown that they have greater solubilizing action with some drugs such as ibuproxam, a poorly water-soluble anti-inflammatory agent.(23,24)

The EINECS number for cyclodextrin is 231-493-2.

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21 Authors

RA Nash.

22 Date of Revision

23 August 2005.

Cyclomethicone

1 Nonproprietary Names

USPNF: Cyclomethicone

2 Synonyms

Dimethylcyclopolysiloxane; *Dow Corning 245 Fluid*; *Dow Corning 246 Fluid*; *Dow Corning 345 Fluid*.

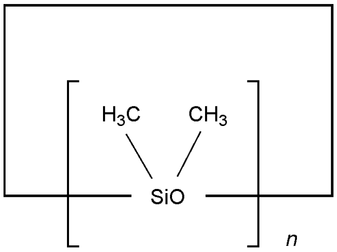
3 Chemical Name and CAS Registry Number

Cyclopolydimethylsiloxane [69430-24-6]

4 Empirical Formula and Molecular Weight

The USPNF 23 describes cyclomethicone as a fully methylated cyclic siloxane containing repeating units of the formula $[-(CH_3)_2SiO-]_n$ in which n is 4, 5, or 6, or a mixture of them.

5 Structural Formula



6 Functional Category

Emollient; humectant; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Cyclomethicone is mainly used in topical pharmaceutical and cosmetic formulations such as water-in-oil creams.(1–3)

Cyclomethicone has been used in cosmetic formulations, at concentrations of 0.1–50%, since the late 1970s and is now the most widely used silicone in the cosmetics industry. Its high volatility, and mild solvent properties, make it ideal for use in topical formulations because its low heat of vaporization means that when applied to skin it has a 'dry' feel.

See also Dimethicone.

8 Description

Cyclomethicone occurs as a clear, colorless and tasteless volatile liquid.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for cyclomethicone.

Test	USPNF 23
Identification	+
Limit of nonvolatile residue	⩽0.15%
Assay of $(C_2H_6OSi)_n$ calculated as the sum of cyclomethicone 4, cyclomethicone 5, and cyclomethicone 6	⩾98.0%
Assay of individual cyclomethicone components	95.0–105.0%

10 Typical Properties

Solubility: soluble in ethanol (95%), isopropyl myristate, isopropyl palmitate, mineral oil, and petrolatum at 80°C; practially insoluble in glycerin, propylene glycol, and water.

See also Table II.

11 Stability and Storage Conditions

Cyclomethicone should be stored in an airtight container in a cool, dry, place.

12 Incompatibilities

—

13 Method of Manufacture

Cyclomethicone is manufactured by the distillation of crude polydimethylsiloxanes.

14 Safety

Cyclomethicone is generally regarded as a relatively nontoxic and nonirritant material. Although it has been used in oral pharmaceutical applications, cyclomethicone is mainly used in topical pharmaceutical formulations. It is also widely used in cosmetics. Studies of the animal and human toxicology of cyclomethicone suggest that it is nonirritant and not absorbed through the skin. Only small amounts are absorbed orally; an acute oral dose in rats produced no deaths.(4,5)

See also Dimethicone.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral powder for reconstitution). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

Table II: Typical physical properties of selected commercially available cyclomethicones.

Grade	Boiling point (°C)	Flash point (°C)	Freezing point (°C)	Refractive index at 25°C	Surface tension (mN/m)	Specific gravity at 25°C	Viscosity (kinematic) (mm^2/s)	Water content (%)
Dow Corning 245 Fluid	205	77	<−50	1.397	18.0	0.95	4.0	0.025
Dow Corning 246 Fluid	245	93	<−40	1.402	18.8	0.96	6.8	0.025
Dow Corning 345 Fluid	217	77	<−50	1.398	20.8	0.957	6.0	0.025

17 Related Substances

Dimethicone; simethicone.

18 Comments

–

19 Specific References

1 Goldenberg RL, Tassof JA, DiSapio AJ. Silicones in clear formulations. *Drug Cosmet Ind* 1986; **138**(Feb): 34, 38, 40, 44.

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20 General References

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21 Authors

RT Guest.

22 Date of Revision

22 August 2005.

Denatonium Benzoate

1 Nonproprietary Names

USPNF: Denatonium benzoate

2 Synonyms

Bitrex; *Bitterguard*; *N*-[2-(2,6-dimethylphenyl)amino]-2-oxoethyl]-*N*,*N*-diethylbenzenemethanaminium benzoate monohydrate; lignocaine benzyl benzoate.

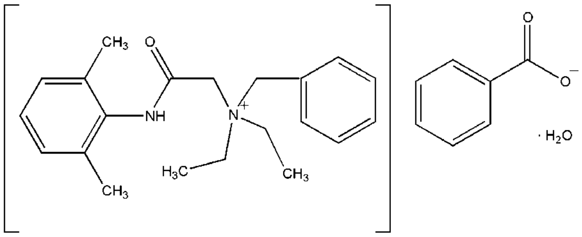
3 Chemical Name and CAS Registry Number

Benzyldiethyl[(2,6-xylylcarbamolyl)methyl]ammonium benzoate anhydrous [3734-33-6]
Benzyldiethyl[(2,6-xylylcarbamolyl)methyl]ammonium benzoate monohydrate [86398-53-0]

4 Empirical Formula and Molecular Weight

$C_{28}H_{34}N_2O_3$	446.59 (for anhydrous)
$C_{28}H_{34}N_2O_3 \cdot H_2O$	464.60 (for monohydrate)

5 Structural Formula



6 Functional Category

Alcohol denaturant; flavoring agent.

7 Applications in Pharmaceutical Formulation or Technology

Denatonium benzoate is among the most bitter of substances known and is detectable at concentrations of approximately 10 ppb. In pharmaceutical and other industrial applications it is added to some products as a deterrent to accidental ingestion.(1–4) It is most commonly used at levels of 5–500 ppm. Denatonium benzoate may also be used to replace brucine or quassin as a denaturant for ethanol.

In pharmaceutical formulations, denatonium benzoate has been used as a flavoring agent in placebo tablets, and in a topical formulation it has been used in an anti-nailbiting preparation.(5)

8 Description

Denatonium benzoate occurs as an odorless, very bitter tasting, white crystalline powder or granules.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for denatonium benzoate.

Test	USPNF 23
Identification	+
Melting range	163–170°C
pH (3% aqueous solution)	6.5–7.5
Loss on drying (monohydrate)	⩽3.5–4.5%
Loss on drying (anhydrous)	⩽1.0%
Residue on ignition	⩽0.1%
Chloride	⩽0.2%
Assay (dried substance)	99.5–101.0%

10 Typical Properties

Density (bulk): 0.3–0.6 g/cm^3
Density (tapped): 0.4–0.7 g/cm^3
Solubility: very soluble in chloroform, and methanol; soluble in ethanol (95%), and water; sparingly soluble in acetone; practically insoluble in ether.

11 Stability and Storage Conditions

Denatonium benzoate is stable up to 140°C and over a wide pH range. It should be stored in a well-closed container (such as polythene-lined steel) in a cool, dry place. Aqueous or alcoholic solutions retain their bitterness for several years even when exposed to light.

12 Incompatibilities

Denatonium benzoate is incompatible with strong oxidizing agents.

13 Method of Manufacture

Denatonium benzoate was first synthesized in the 1950s and is usually prepared by reacting denatonium chloride with benzyl benzoate.

14 Safety

Denatonium benzoate is generally regarded as a nonirritant and nonmutagenic substance. However, there has been a single report of contact urticaria attributed to denatonium benzoate occurring in a 30-year-old man who developed asthma and pruritus after using an insecticidal spray denatured with denatonium benzoate.(6)

LD_{50} (rabbit, oral): 0.508 g/kg(7)
LD_{50} (rat, oral): 0.584 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Containers should be kept tightly closed and handled in areas with good ventilation. Eye protection, gloves, and a dust mask are recommended. Denatonium benzoate is moderately toxic by ingestion and when heated to decomposition emits toxic vapors of NO_x. Denatonium benzoate may also cause hypersensitization.

16 Regulatory Status

Denatonium benzoate is used worldwide as a denaturant for alcohol. It is included in the FDA Inactive Ingredients Guide (topical gel and solution).

17 Related Substances

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18 Comments

Several HPLC methods of analysis for denatonium benzoate have been reported.(8–10) The EINECS number for denatonium benzoate is 223-095-2.

19 Specific References

1 Klein-Schwartz W. Denatonium benzoate: review of efficacy and safety. *Vet Hum Toxicol* 1991; **33**(6): 545–547.

2 Sibert JR, Frude N. Bittering agents in the prevention of accidental poisoning: children's reactions to denatonium benzoate (Bitrex). *Arch Emerg Med* 1991; **8**(1): 1–7.

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20 General References

Payne HAS. Bitrex – a bitter solution to safety. *Chem Ind* 1988; **22**: 721–723.

Payne HAS. Bitrex – a bitter solution to product safety. *Drug Cosmet Ind* 1989; **144**(May): 30, 32, 34.

21 Authors

PJ Weller.

22 Date of Revision

14 August 2005.

Dextrates

1 Nonproprietary Names

USPNF: Dextrates

2 Synonyms

Candex; *Emdex*.

3 Chemical Name and CAS Registry Number

Dextrates [39404-33-6]

4 Empirical Formula and Molecular Weight

The USPNF 23 describes dextrates as a purified mixture of saccharides resulting from the controlled enzymatic hydrolysis of starch. It may be either hydrated or anhydrous. Its dextrose equivalent is not less than 93.0% and not more than 99.0%, calculated on the dried basis.

5 Structural Formula

See Section 4.

6 Functional Category

Tablet binder; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Dextrates is a directly compressible tablet diluent used in chewable, nonchewable, soluble, dispersible, and effervescent tablets.(1–3) It is a free-flowing material and glidants are thus unnecessary. Lubrication with magnesium stearate (0.5–1.0% w/w) is recommended.(4) Dextrates may also be used as a binding agent by the addition of water, no further binder being required.(4)

Tablets made from dextrates increase in crushing strength in the first few hours after manufacture, but no further increase occurs on storage.(5)

8 Description

Dextrates is a purified mixture of saccharides resulting from the controlled enzymatic hydrolysis of starch. It is either anhydrous or hydrated. In addition to dextrose, dextrates contains 3–5% w/w maltose and higher polysaccharides.

Dextrates comprises white spray-crystallized free-flowing porous spheres. It is odorless with a sweet taste (about half as sweet as sucrose).

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for dextrates.

Test	USPNF 23
pH (20% aqueous solution)	3.8–5.8
Loss on drying	
Anhydrous	⩽2.0%
Hydrated	7.8–9.2%
Residue on ignition	⩽0.1%
Heavy metals	⩽5 ppm
Organic volatile impurities	+
Dextrose equivalent (dried basis)	93.0–99.0%

10 Typical Properties

Angle of repose: 26.4° (6)

Compressibility: *see* Figure 1.(6)

Density (bulk): 0.68 g/cm^3(6)

Density (tapped): 0.72 g/cm^3(6)

Density (true): 1.539 g/cm^3

Hausner ratio: 1.05

Flowability: 9.3 g/s (6)

Heat of combustion: 16.8–18.8 J/g (4.0–4.5 cal/g)

Heat of solution: −105 J/g (–25 cal/g)

Melting point: 141°C.

Moisture content: 7.8–9.2% w/w (hydrated form). *See also* Figure 2.(7)

Particle size distribution: not more than 3% retained on a 840 μm sieve; not more than 25% passes through a 150 μm sieve. Mean particle size 190–220 μm.

Solubility: soluble 1 in 1 part of water; insoluble in ethanol (95%), propan-2-ol, and common organic solvents.

Specific surface area: 0.70 m^2/g

11 Stability and Storage Conditions

Dextrates may be heated to 50°C without any appreciable darkening of color. Dextrates should be stored in a well-closed container in conditions that do not exceed 25°C and 60% relative humidity. When correctly stored in unopened containers, dextrates has a shelf-life of 3 years.

12 Incompatibilities

At high temperatures and humidities, dextrates may react with substances containing a primary amino group (Maillard reaction).(8,9) Also incompatible with oxidizing agents.

13 Method of Manufacture

Dextrates is produced by controlled enzymatic hydrolysis of starch. The product is spray-crystallized, and may be dried to produce an anhydrous form.

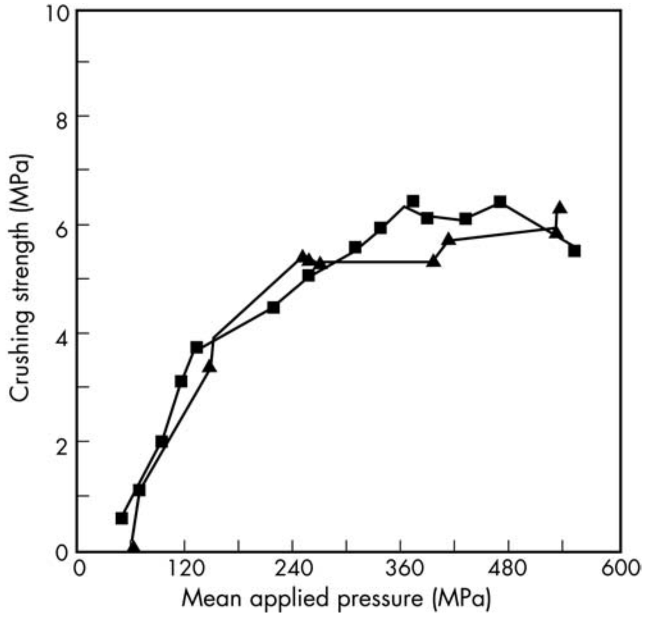

Figure 1: Crushing strength for dextrates.
■: Dextrates, *Emdex* (Lot # L-53X, Mendell) at *V* = 100 mm/s
▲: Dextrates, *Emdex* (Lot # L-53X, Mendell) at *V* = 300 mm/s

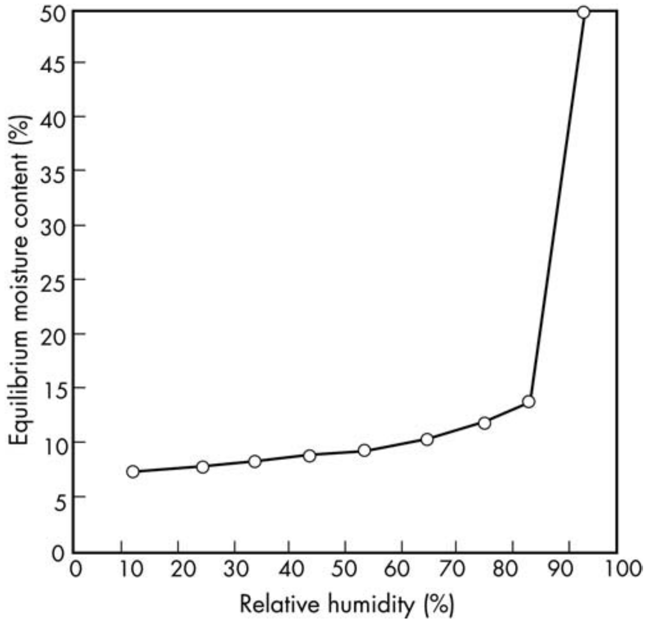

Figure 2: Equilibrium moisture content of dextrates at 25°C.[7]

14 Safety

Dextrates is used in oral pharmaceutical formulations and is generally regarded as a relatively nontoxic and nonirritant material.

15 Handling Precautions

Observe normal handling precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredient Guide (oral; tablets, sustained action). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Dextrose.

18 Comments

Only the hydrated form of dextrates is currently commercially available.

19 Specific References

1 Henderson NL, Bruno AJ. Lactose USP (Beadlets) and Dextrose (PAF 2011): two new agents for direct compression. *J Pharm Sci* 1970; **59**: 1336–1340.
2 Shukla AJ, Price JC. Effect of moisture content on compression properties of two dextrose-based directly compressible diluents. *Pharm Res* 1991; **8**(3): 336–340.
3 Allen LV. Featured excipient: capsule and tablet diluents. *Int J Pharm Compound* 2000; **4**(4): 306–310, 324–325.
4 Penwest. Technical Literature: *Emdex*, 2004.
5 Shangraw RF, Wallace JW, Bowers FM. Morphology and functionality in tablet excipients by direct compression: Part I. *Pharm Technol* 1981; **5**(9): 69–78.
6 Celik M, Okutgen E. A feasibility study for the development of a prospective compaction functionality test and the establishment of a compaction data bank. *Drug Dev Ind Pharm* 1993; **19**: 2309–2334.
7 Callahan JC, Cleary GW, Elefant M, *et al*. Equilibrium moisture content of pharmaceutical excipients. *Drug Dev Ind Pharm* 1982; **8**(3): 355–369.
8 Blang SM, Huang WT. Interaction of dexamphetamine sulphate with dextrates in solution. *J Pharm Sci* 1973; **62**(4): 652–655.
9 Blaug SM, Huang WT. Browning of dextrates in solid-solid mixtures containing dexamphetamine sulfate. *J Pharm Sci* 1974; **63**(9): 1415–1418.

20 General References

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Shangraw RF. Direct compression tabletting. In: Swarbrick J, Boylan JC, eds. *Encyclopedia of Pharmaceutical Technology,* vol. **4**. New York: Marcel Dekker, 1988: 85–106.

21 Authors

NA Armstrong.

22 Date of Revision

16 August 2005.

Dextrin

1 Nonproprietary Names

BP: Dextrin
JP: Dextrin
PhEur: Dextrinum
USPNF: Dextrin

2 Synonyms

Avedex; British gum; *Caloreen*; canary dextrin; *C*Pharm*; *Crystal Gum*; dextrinum album; *Primogran W*; starch gum; yellow dextrin; white dextrin.

3 Chemical Name and CAS Registry Number

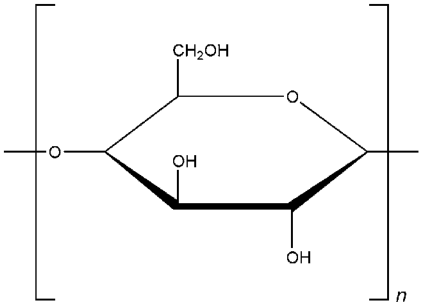
Dextrin [9004-53-9]

4 Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n \cdot xH_2O$ $(162.14)_n$

The molecular weight of dextrin is typically 4500–85 000 and depends on the number of $(C_6H_{10}O_5)$ units in the polymer chain.

5 Structural Formula



6 Functional Category

Stiffening agent; suspending agent; tablet binder; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Dextrin is a dextrose polymer used as an adhesive and stiffening agent for surgical dressings. It is also used as a tablet and capsule diluent; as a binder for tablet granulation; as a sugar-coating ingredient that serves as a plasticizer and adhesive; and as a thickening agent for suspensions.

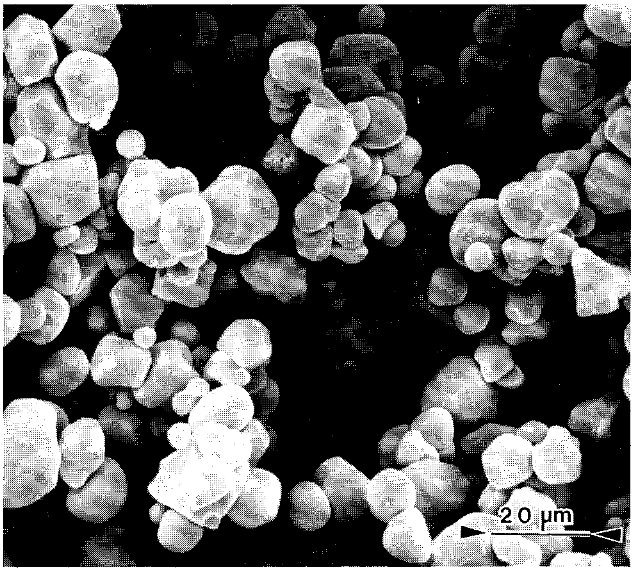
Additionally, dextrin has been used as a source of carbohydrate by people with special dietary requirements because it has a low electrolyte content and is free of lactose and sucrose.$^{(1)}$

Dextrin is also used in cosmetics.

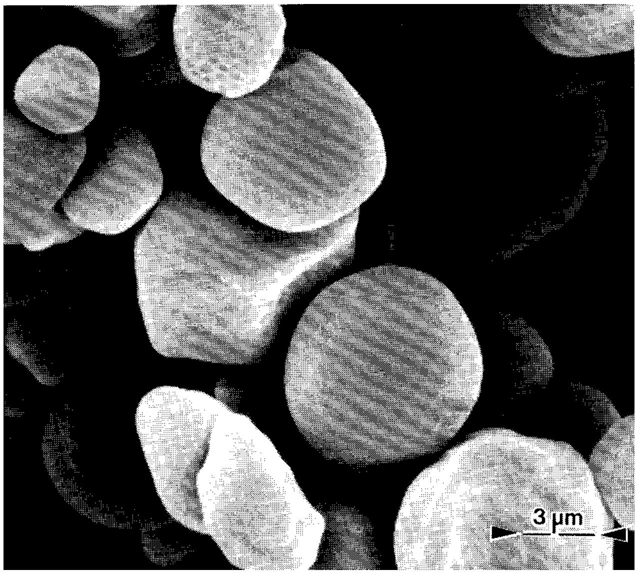
8 Description

Dextrin is partially hydrolyzed maize (corn) or potato starch. It is a white, pale yellow or brown-colored powder with a slight characteristic odor.

SEM: 1
Excipient: Dextrin
Manufacturer: Matheson Colleman & Bell
Magnification: 600×



SEM: 2
Excipient: Dextrin
Manufacturer: Matheson Colleman & Bell
Magnification: 2400×



9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for dextrin.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Appearance of solution	+	—	—
Loss on drying	⩽10.0%	⩽13.0%	⩽13.0%
Acidity	+	+	+
Residue on ignition	⩽0.5%	⩽0.5%	⩽0.5%
Chloride	⩽0.013%	⩽0.2%	⩽0.2%
Sulfate	⩽0.019%	—	—
Oxalate	+	—	—
Calcium	+	—	—
Heavy metals	⩽50 ppm	⩽20 ppm	⩽20 μg/g
Protein	—	—	⩽1.0%
Organic volatile impurities	—	—	+
Reducing sugars/substances (calculated as $C_6H_{12}O_6$)	—	⩽10.0%	⩽10.0%

10 Typical Properties

Acidity/alkalinity: pH = 2.8–8.0 for a 5% w/v aqueous solution.
Density (bulk): 0.80 g/cm^3
Density (tapped): 0.91 g/cm^3
Density (true): 1.495–1.589 g/cm^3
Melting point: 178°C (with decomposition)
Moisture content: 5% w/w
Particle size distribution: *see* Figure 1.
Solubility: practically insoluble in chloroform, ethanol (95%), ether, and propan-2-ol; slowly soluble in cold water; very soluble in boiling water, forming a mucilaginous solution.
Specific surface area: 0.14 m^2/g

11 Stability and Storage Conditions

Physical characteristics of dextrin may vary slightly depending on the method of manufacture and on the source material. In aqueous solutions, dextrin molecules tend to aggregate as density, temperature, pH, or other characteristics change. An increase in viscosity is caused by gelation or retrogradation as dextrin solutions age, and is particularly noticeable in the less-soluble maize starch dextrins. Dextrin solutions are thixotropic, becoming less viscous when sheared but changing to a soft paste or gel when allowed to stand. However, acids that are present in dextrin as residues from manufacturing can cause further hydrolysis, which results in a gradual thinning of solutions. Residual acid, often found in less-soluble dextrins such as pyrodextrin, will also cause a reduction in viscosity during dry storage. To eliminate these problems, dextrin manufacturers neutralize dextrins of low solubility with ammonia or sodium carbonate in the cooling vessel.

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatible with strong oxidizing agents.

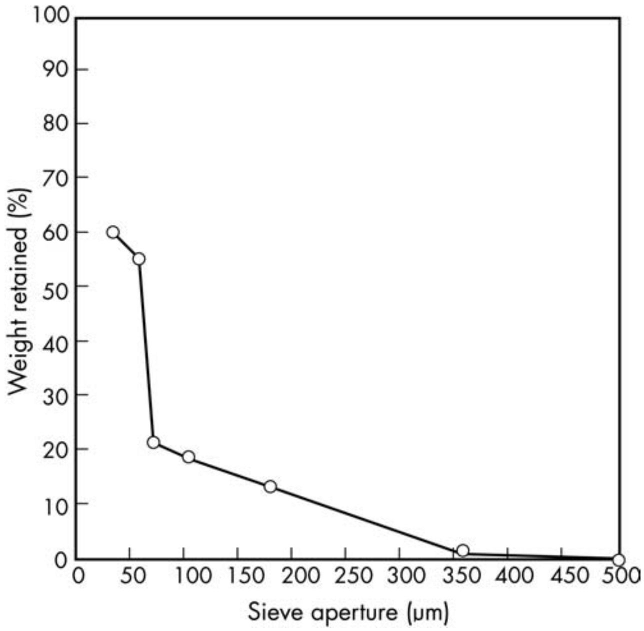


Figure 1: Particle size distribution of dextrin.

13 Method of Manufacture

Dextrin is prepared by the incomplete hydrolysis of starch by heating in the dry state with or without the aid of suitable acids and buffers; moisture may be added during heating. The PhEur 2005 specifies that dextrin is derived from maize (corn) or potato starch. A specification for cassava is included in the USPNF 23.

14 Safety

Dextrin is generally regarded as a nontoxic and nonirritant material at the levels employed as an excipient. Larger quantities are used as a dietary supplement without adverse effects, although ingestion of very large quantities may be harmful.

LD$_{50}$ (mouse, IV): 0.35 g/kg(2)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Dextrin may be irritant to the eyes. Eye protection, gloves, and a dust mask are recommended.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (IV injections, oral tablets and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Dextrates; dextrose; glucose liquid; maltodextrin.

See also Section 18.

18 Comments

Dextrin is available from suppliers in a number of modified forms and mixtures such as dextrimaltose, a mixture of maltose and dextrin obtained by the enzymatic action of barley malt on corn flour. It is a light, amorphous powder, readily soluble in milk or water.

Crystal Gum is a grade of dextrin containing carbohydrate not less than 98% of dry weight. *Caloreen*(1) is a water-soluble mixture of dextrins consisting predominantly of polysaccharides containing an average of 5 dextrose molecules, with a mean molecular weight of 840, that does not change after heating. A 22% w/v solution of *Caloreen* is isoosmotic with serum.

A specification for dextrin is contained in the Food Chemicals Codex (FCC).

The EINECS number for dextrin is 232-675-4.

19 Specific References

1 Berlyne GM, Booth EM, Brewis RAL, *et al*. A soluble glucose polymer for use in renal failure and calorie-deprivation states. *Lancet* 1969; i: 689–692.

2 Sweet DV, ed. *Registry of Toxic Effects of Chemical Substances*. Cincinnati: US Department of Health, 1987: 1859.

20 General References

French D. Chemical and physical properties of starch. *J Animal Sci* 1973; **37**: 1048–1061.

Satterthwaite RW, Iwinski DJ. Starch dextrins. In: Whistler RL, Bemiller JN, eds. *Industrial Gums*. New York: Academic Press, 1973: 577–599.

21 Authors

A Day.

22 Date of Revision

17 August 2005.

Dextrose

1 Nonproprietary Names

BP: Glucose monohydrate
JP: Glucose
PhEur: Glucosum monohydricum
USP: Dextrose

2 Synonyms

Blood sugar; *Caridex*; corn sugar; *C*PharmDex*; *Dextrofin*; D-(+)-glucopyranose monohydrate; grape sugar; *Lycadex PF*; *Roferose*; starch sugar; *Tabfine D-100*.

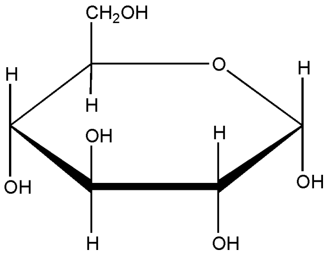
3 Chemical Name and CAS Registry Number

D-(+)-Glucose monohydrate [5996-10-1]
See also Section 17.

4 Empirical Formula and Molecular Weight

$C_6H_{12}O_6 \cdot H_2O$ 198.17 (for monohydrate)
See also Section 17.

5 Structural Formula



Anhydrous material shown.

6 Functional Category

Tablet and capsule diluent; therapeutic agent; tonicity agent; sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

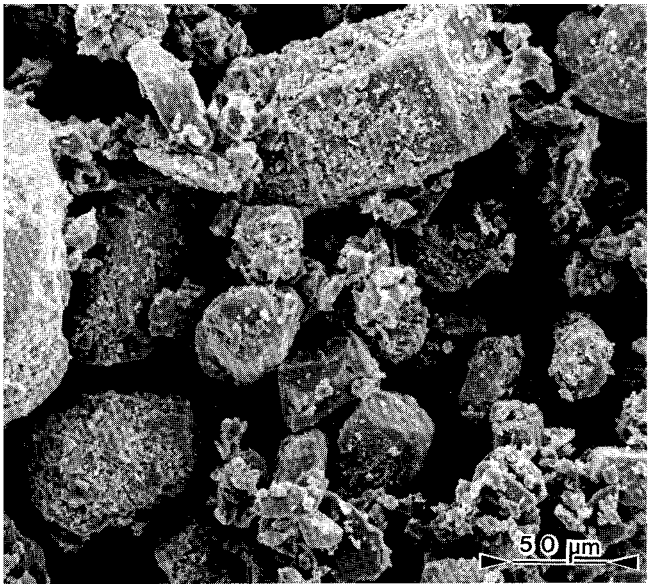
Dextrose is widely used in solutions to adjust tonicity and as a sweetening agent. Dextrose is also used as a wet granulation diluent and binder, and as a direct-compression tablet diluent and binder, primarily in chewable tablets. Although dextrose is comparable as a tablet diluent to lactose, tablets produced with dextrose monohydrate require more lubrication, are less friable, and have a tendency to harden.(1–3) The mildly reducing properties of dextrose may be used when tableting to improve the stability of active materials that are sensitive to oxidation.

Dextrose is also used therapeutically and is the preferred source of carbohydrate in parenteral nutrition regimens.

8 Description

Dextrose occurs as odorless, sweet-tasting, colorless crystals or as a white crystalline or granular powder. The JP 2001 describes dextrose as dextrose anhydrous; the PhEur 2005 specifies dextrose as either dextrose anhydrous or dextrose monohydrate; and the USP 28 specifies dextrose as dextrose monohydrate.

SEM: 1
Excipient: Dextrose anhydrous (granular)
Manufacturer: Mallinckrodt Specialty Chemicals Co.
Lot No.: KLKZ
Magnification: 180×



9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Data are shown for dextrose monohydrate; *see* Section 17 for data for dextrose anhydrous.

Acidity/alkalinity: pH = 3.5–5.5 (20% w/v aqueous solution)
Density (bulk): 0.826 g/cm^3
Density (tapped): 1.020 g/cm^3
Density (true): 1.54 g/cm^3
Heat of solution: 105.4 J/g (25.2 cal/g)
Melting point: 83°C
Moisture content: anhydrous dextrose absorbs significant amounts of moisture at 25°C and a relative humidity of about 85% to form the monohydrate. The monohydrate similarly only absorbs moisture at around 85% relative humidity and 25°C. *See* Figure 1.

Table I: Pharmacopeial specifications for dextrose.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	—	+	—
Color of solution	+	+	+
Specific optical rotation	—	+52.5° to +53.3°	+52.6° to +53.2°
Acidity	+	+	+
Organic volatile impurities	—	—	+
Water			
for monohydrate	—	7.0–9.5%	7.5–9.5%
for anhydrous	≤1.0%	—	≤0.5%
Residue on ignition	≤0.1%	≤0.1%	≤0.1%
Chloride	≤0.018%	≤125 ppm	≤0.018%
Sulfate	≤0.024%	≤200 ppm	≤0.025%
Arsenic	≤1.3 ppm	≤1 ppm	≤1 ppm
Barium	—	+	—
Calcium	—	≤200 ppm	—
Heavy metals	≤4 ppm	—	≤5 ppm
Lead	—	≤0.5 ppm	—
Dextrin	+	+	+
Soluble starch, and sulfites	+	+	+
Pyrogens(a)	—	+	—
Assay (dried basis)	≥99.5%	—	—

(a) If intended for large volume parenteral use.

Table II: Solubility of dextrose monohydrate.

Solvent	Solubility at 20°C
Chloroform	Practically insoluble
Ethanol (95%)	1 in 60
Ether	Practically insoluble
Glycerin	Soluble
Water	1 in 1

Osmolarity: a 5.51% w/v aqueous solution is isoosmotic with serum. However, it is not isotonic since dextrose can pass through the membrane of red cells and cause hemolysis.

Solubility: *see* Table II.

11 Stability and Storage Conditions

Dextrose has good stability under dry storage conditions. Aqueous solutions may be sterilized by autoclaving. However, excessive heating can cause a reduction in pH and caramelization of solutions.(4–7)

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Dextrose solutions are incompatible with a number of drugs such as cyanocobalamin, kanamycin sulfate, novobiocin sodium, and warfarin sodium.(8) Erythromycin gluceptate is unstable in dextrose solutions at a pH less than 5.05.(9) Decomposition of B-complex vitamins may occur if they are warmed with dextrose.

In the aldehyde form, dextrose can react with amines, amides, amino acids, peptides, and proteins. Brown coloration and decomposition occur with strong alkalis.

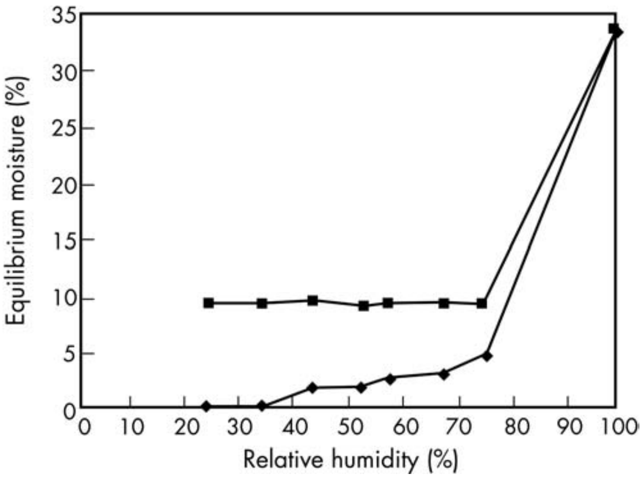


Figure 1: Sorption–desorption isotherm for anhydrous dextrose granules.
◆: Sorption
■: Desorption

Dextrose may cause browning of tablets containing amines (Maillard reaction).

13 Method of Manufacture

Dextrose, a monosaccharide sugar, occurs widely in plants and is manufactured on a large scale by the acid or enzymatic hydrolysis of starch, usually maize (corn) starch. Below 50°C α-D-dextrose monohydrate is the stable crystalline form produced; above 50°C the anhydrous form is obtained; and at still higher temperatures β-D-dextrose is formed, which has a melting point of 148–155°C.

14 Safety

Dextrose is rapidly absorbed from the gastrointestinal tract. It is metabolized to carbon dioxide and water with the release of energy.

Concentrated dextrose solutions given by mouth may cause nausea and vomiting. Dextrose solutions of concentration greater than 5% w/v are hyperosmotic and are liable to cause local vein irritation following intravenous administration. Thrombophlebitis has been observed following the intravenous infusion of isoosmotic dextrose solution with low pH, probably owing to the presence of degradation products formed by overheating during sterilization. The incidence of phlebitis may be reduced by adding sufficient sodium bicarbonate to raise the pH of the infusion above pH 7.

LD_{50} (mouse, IV): 9 g/kg(10)
LD_{50} (rat, oral): 25.8 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Dust generation should be minimized to reduce the risk of explosion.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (capsules; inhalations; IM, IV, and SC injections; tablets, oral solutions, and syrups). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Dextrates; dextrin; dextrose anhydrous; fructose; glucose liquid; polydextrose; sucrose.

Dextrose anhydrous

Empirical formula: $C_6H_{12}O_6$
Molecular weight: 180.16
CAS number: [50-99-7]
Synonyms: anhydrous dextrose; anhydrous D-(+)-glucopyranose; anhydrous glucose; dextrosum anhydricum.
Appearance: white, odorless, crystalline powder with a sweet taste.
Acidity/alkalinity: pH = 5.9 (10% w/v aqueous solution)
Density (bulk): 1.3–1.4 g/cm^3
Density (tapped): 1.1–1.2 g/cm^3
Melting point: 146°C
Moisture content: *see* Section 10.
Osmolarity: a 5.05% w/v aqueous solution is isoosmotic with serum. *See also* Section 10.
Refractive index: n_D^{20} = 1.3479 (10% w/v aqueous solution)
Solubility: *see* Table III.
Specific gravity: *see* Table IV.
Specific surface area: 0.22–0.29 m^2/g

Table III: Solubility of dextrose anhydrous.

Solvent	Solubility at 20°C unless otherwise stated
Ethanol (95%)	Sparingly soluble
Ether	Sparingly soluble
Methanol	1 in 120
Water	1 in 1.1 at 25°C
	1 in 0.8 at 30°C
	1 in 0.41 at 50°C
	1 in 0.28 at 70°C
	1 in 0.18 at 90°C

Table IV: Specific gravity of dextrose anhydrous aqueous solutions.

Concentration of aqueous dextrose solution (% w/v)	Specific gravity at 17.5°C
5	1.019
10	1.038
20	1.076
30	1.113
40	1.149

18 Comments

The way in which the strengths of dextrose solutions are expressed varies from country to country. The JP 2001 requires strengths to be expressed in terms of dextrose monohydrate, while the BP 2004 and USP 28 require strengths to be expressed in terms of anhydrous dextrose. Approximately 1.1 g of dextrose monohydrate is equivalent to 1 g of anhydrous dextrose.

A specification for dextrose is contained in the Food Chemicals Codex (FCC).

The EINECS number for dextrose is 200-075-1.

19 Specific References

1 DuVall RN, Koshy KT, Dashiell RE. Comparative evaluation of dextrose and spray-dried lactose in direct compression systems. *J Pharm Sci* 1965; **54**: 1196–1200.
2 Henderson NL, Bruno AJ. Lactose USP (beadlets) and dextrose (PAF 2011): two new agents for direct compression. *J Pharm Sci* 1970; **59**: 1336–1340.
3 Armstrong NA, Patel A, Jones TM. The compressional properties of dextrose monohydrate and anhydrous dextrose of varying water contents. In: Rubinstein MH, ed. *Pharmaceutical Technology: Tableting Technology*, vol. **1**. Chichester: Ellis Horwood, 1987: 127–138.
4 Wing WT. An examination of the decomposition of dextrose solution during sterilisation. *J Pharm Pharmacol* 1960; **12**: 191T–196T.
5 Murty BSR, Kapoor JN, Smith FX. Levels of 5-hydroxymethylfurfural in dextrose injection. *Am J Hosp Pharm* 1977; **34**: 205–206.
6 Sturgeon RJ, Athanikar NK, Harbison HA, *et al.* Degradation of dextrose during heating under simulated sterilization. *J Parenter Drug Assoc* 1980; **34**: 175–182.
7 Durham DG, Hung CT, Taylor RB. Identification of some acids produced during autoclaving of D-glucose solutions using HPLC. *Int J Pharm* 1982; **12**: 31–40.
8 Patel JA, Phillips GL. A guide to physical compatibility of intravenous drug admixtures. *Am J Hosp Pharm* 1966; **23**: 409–411.
9 Edward M. pH – an important factor in the compatibility of additives in intravenous therapy. *Am J Hosp Pharm* 1967; **24**: 440–449.
10 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 1860–1861.

20 General References

—

21 Authors

A Day.

22 Date of Revision

9 June 2005.

Dibutyl Phthalate

1 Nonproprietary Names

BP: Dibutyl phthalate
PhEur: Dibutylis phthalas

2 Synonyms

Araldite 502; benzenedicarboxylic acid; benzene-*o*-dicarboxylic acid di-*n*-butyl ester; butyl phthalate; *Celluflex DBP*; DBP; dibutyl 1,2-benzenedicarboxylate; dibutyl benzene 1,2-dicarboxylate; dibutyl ester of 1,2-benzenedicarboxylic acid; dibutyl-*o*-phthalate; di-*n*-butyl phthalate; *Elaol*; *Ergoplast FDB*; *Genoplast B*; *Hatcol DBP*; *Hexaplast M/B*; *Kodaflex DBP*; *Monocizer DBP*; *Palatinol C*; phthalic acid dibutyl ester; *Polycizer DBP*; *PX 104*; *RC Plasticizer DBP*; *Staflex DBP*; *Unimoll DB*; *Vestimol C*; *Witcizer 300*.

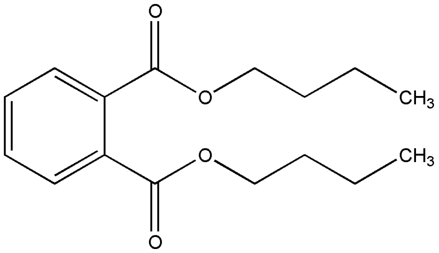
3 Chemical Name and CAS Registry Number

Dibutyl benzene-1,2-dicarboxylate [84-74-2]

4 Empirical Formula and Molecular Weight

$C_{16}H_{22}O_4$ 278.34

5 Structural Formula



6 Functional Category

Film-former; plasticizer; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Dibutyl phthalate is used in pharmaceutical formulations as a plasticizer in film-coatings. It is also used extensively as a solvent particularly in cosmetic formulations such as antiperspirants, hair shampoos and hair sprays. In addition to a number of industrial applications, dibutyl phthalate is used as an insect repellent, although it is not as effective as dimethyl phthalate.

8 Description

Dibutyl phthalate occurs as an odorless, oily, colorless, or very slightly yellow-colored, viscous liquid.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for dibutyl phthalate.

Test	PhEur 2005
Identification	+
Characters	+
Appearance	+
Relative density	1.043–1.048
Refractive index	1.490–1.495
Acidity	+
Related substances	+
Water	⩽0.2%
Sulfated ash	⩽0.1%
Assay	99.0–101.0%

10 Typical Properties

Boiling point: 340°C
Density: *see* Table II.
Flash point: 171°C open cup.
Melting point: −35°C
Partition coefficient:
Octanol : water $\log k_{ow} = 4.50$
Refractive index: $n_D^{20} = 1.491–1.495$
Solubility: very soluble in acetone, benzene, ethanol (95%), and ether; soluble 1 in 2500 of water at 20°C.
Viscosity (dynamic): *see* Table II.

Table II: Density and dynamic viscosity of dibutyl phthalate at specified temperatures.

Temperature (°C)	Density (g/cm^3)	Dynamic viscosity (mPa s)
0	1.0627	59
10	1.0546	33
20	1.0465	20
30	1.0384	13
40	1.0303	9
50	1.0222	7

11 Stability and Storage Conditions

Dibutyl phthalate should be stored in a well-closed container in a cool, dry, location. Containers may be hazardous when empty since they can contain product residues such as vapors and liquids.

12 Incompatibilities

Dibutyl phthalate reacts violently with chlorine. It also reacts with oxidizing agents, acids, bases, and nitrates.

13 Method of Manufacture

Dibutyl phthalate is produced from *n*-butanol and phthalic anhydride in an ester formation reaction.

14 Safety

Dibutyl phthalate is generally regarded as a relatively nontoxic material, although it has occasionally been reported to cause hypersensitivity reactions. It is widely used in topical cosmetic and some oral pharmaceutical formulations.

LD_{50} (mouse, IV): 0.72 g/kg⁽¹⁾
LD_{50} (mouse, oral): 5.3 g/kg
LD_{50} (rat, oral): 8.0 g/kg
LD_{50} (rat, IP): 3.05 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Contact with the skin and eyes should be avoided. Decomposition produces toxic fumes, carbon monoxide and carbon dioxide.

In the USA, the permitted 8-hour exposure limit for dibutyl phthalate is 5 mg/m^3. In the UK, the long-term (8-hour TWA) exposure limit for dibutyl phthalate is 5 mg/m^3. The short-term (15-minute) exposure limit is 10 mg/m^3.(2)

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral delayed action, enteric coated, tablets). Included in nonparenteral medicines licensed in the UK (oral capsules, tablets, granules; topical creams and solutions).

17 Related Substances

Diethyl phthalate; dimethyl phthalate; dioctyl phthalate.

Dioctyl phthalate

Empirical formula: $C_{24}H_{38}O_4$
Molecular weight: 390.55
CAS number: dioctyl phthalate occurs commercially in two isomeric forms: di-*n*-octyl phthalate [117-84-0] and di(2-ethylhexyl) phthalate [117-81-7].
Synonyms: 1,2-benzenedicarboxylic acid bis(2-ethylhexyl) ester; bis(2-ethylhexyl) phthalate; di(2-ethyl-hexyl)phthalate; DEHP; DOP; *Octoil*.
Description: clear, colorless, odorless, and anhydrous liquid.
Boiling point: 384°C
Flash point: 206°C (closed cup).
Melting point: −50°C
Refractive index: $n_D^{20} = 1.50$
Solubility: soluble in conventional organic solvents; practically insoluble in water.
Comments: the EINECS number for dioctyl phthalate is 204-214-7.

18 Comments

The EINECS number for dibutyl phthalate is 201-557-4.

19 Specific References

1 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 1164.
2 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.

20 General References

Wilson AS. *Plasticisers – Principles and Practice*. London: Institute of Materials, 1995.

21 Authors

RT Guest.

22 Date of Revision

21 August 2005.

Dibutyl Sebacate

1 Nonproprietary Names

USPNF: Dibutyl sebacate

2 Synonyms

Butyl sebacate; decanedioic acid, dibutyl ester; dibutyl decanedioate; dibutyl 1,8-octanedicarboxylate; *Kodaflex DBS*.

3 Chemical Name and CAS Registry Number

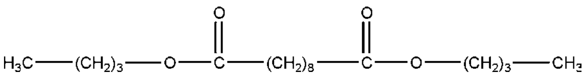
Decanedioic acid, di-*n*-butyl ester [109-43-3]

4 Empirical Formula and Molecular Weight

$C_{18}H_{34}O_4$ 314.47

The USPNF 23 describes dibutyl sebacate as consisting of the esters of *n*-butyl alcohol and saturated dibasic acids, principally sebacic acid.

5 Structural Formula



$$H_3C—(CH_2)_3—O—\overset{\overset{O}{\|}}{C}—(CH_2)_8—\overset{\overset{O}{\|}}{C}—O—(CH_2)_3—CH_3$$

6 Functional Category

Plasticizer.

7 Applications in Pharmaceutical Formulation or Technology

Dibutyl sebacate is used in oral pharmaceutical formulations as a plasticizer for film coatings on tablets, beads, and granules, at concentrations of 10–30% by weight of polymer.(1,2) It is also used as a plasticizer in controlled-release tablets and microcapsule preparations.(3,4)

Dibutyl sebacate is also used as a synthetic flavor and flavor adjuvant in food products; for example, up to 5 ppm is used in ice cream and nonalcoholic beverages.

8 Description

Dibutyl sebacate is a clear, colorless, oily liquid with a bland to slight butyl odor.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for dibutyl sebacate.

Test	USPNF 23
Specific gravity	0.935–0.939
Refractive index	1.429–1.441
Acid value	$\leqslant$0.1
Saponification value	352–357
Assay (of $C_{18}H_{34}O_4$)	$\geqslant$92.0%

10 Typical Properties

Acid value: 0.02
Boiling point: 344–349°C
Flash point: 193°C
Melting point: −10°C
Refractive index: n_D^{25} = 1.4401
Solubility: soluble in ethanol (95%), isopropanol, and mineral oil; practically insoluble in water.
Specific gravity: 0.937 at 20°C
Vapor density (relative): 10.8 (air = 1)
Vapor pressure: 0.4 kPa (3 mmHg) at 180°C

11 Stability and Storage Conditions

Dibutyl sebacate is stable. It is not reactive with water and hazardous polymerization does not occur. Dibutyl sebacate should be stored in a closed container in a cool, dry location.

12 Incompatibilities

Dibutyl sebacate is incompatible with strong oxidizing materials and strong alkalis.

13 Method of Manufacture

Dibutyl sebacate is manufactured by the esterification of *n*-butanol and sebacic acid in the presence of a suitable catalyst, and by the distillation of sebacic acid with *n*-butanol in the presence of concentrated acid.

14 Safety

Dibutyl sebacate is used in cosmetics, foods, and oral pharmaceutical formulations, and is generally regarded as a nontoxic and nonirritant material. Following oral administration, dibutyl sebacate is metabolized in the same way as fats. In humans, direct eye contact and prolonged or repeated contact with the skin may cause very mild irritation. Acute animal toxicity tests and long-term animal feeding studies have shown no serious adverse effects to be associated with orally administered dibutyl sebacate.

LD_{50} (rat, oral): 16 g/kg(5)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. It is recommended that eye protection be used at all times. When heating this product, it is recommended to have a well-ventilated area, and the use of a respirator is advised.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules, granules, film-coated, sustained action, and tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

—

18 Comments

As dibutyl sebacate is an emollient ester, the personal care grade is recommended for use in cosmetics, hair products, lotions, and creams.

The EINECS number for dibutyl sebacate is 203-672-5.

19 Specific References

1 Goodhart FW, Harris MR, Murthy KS, Nesbitt RU. An evaluation of aqueous film-forming dispersions for controlled release. *Pharm Technol* 1984; **8**(4): 64, 66, 68, 70, 71.
2 Iyer U, Hong W-H, Das N, Ghebre-Sellassie I. Comparative evaluation of three organic solvent and dispersion-based ethylcellulose coating formulations. *Pharm Technol* 1990; **14**(9): 68, 70, 72, 74, 76, 78, 80, 82, 84, 86.
3 Lee BJ, Ryn SG, Cui JH. Controlled release of dual drug loaded hydroxypropyl methylcellulose matrix tablet using drug containing polymeric coatings. *Int J Pharm* 1999; **188**: 71–80.
4 Zhang ZY, Ping QN, Xiao B. Microencapsulation and characterization of tramadol-resin complexes. *J Control Release* 2000; **66**: 107–113.
5 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 1165.

20 General References

Appel LE, Zentner GM. Release from osmotic tablets coated with modified Aquacoat lattices. *Proc Int Symp Control Rel Bioact Mater* 1990; **17**: 335–336.
Ozturk AG, Ozturk SS, Palsson BO, *et al*. Mechanism of release from pellets coated with an ethylcellulose-based film. *J Control Release* 1990; **14**: 203–213.
Rowe RC. Materials used in the film coating of oral dosage forms. In: Florence AT, ed. *Materials Used in Pharmaceutical Formulation: Critical Reports on Applied Chemistry*, vol. **6**. Oxford: Blackwell Scientific, 1984: 1–36.
Wheatley TA, Steurnagel CR. Latex emulsions for controlled drug delivery. In: McGinity JC, ed. *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*, 2nd edn. New York: Marcel Dekker, 1996: 13–41.

21 Authors

SW Kennedy.

22 Date of Revision

15 August 2005.

Diethanolamine

1 Nonproprietary Names

USPNF: Diethanolamine

2 Synonyms

Bis(hydroxyethyl)amine; DEA; diethylolamine; 2,2′-dihydroxydiethylamine; diolamine; 2,2′-iminodiethanol.

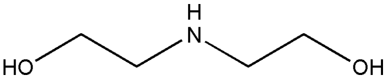
3 Chemical Name and CAS Registry Number

2,2′-Iminobisethanol [111-42-2]

4 Empirical Formula and Molecular Weight

$C_4H_{11}NO_2$ 105.14

5 Structural Formula



6 Functional Category

Alkalizing agent; emulsifying agent.

7 Applications in Pharmaceutical Formulation or Technology

Diethanolamine is primarily used in pharmaceutical formulations as a buffering agent, such as in the preparation of emulsions with fatty acids. In cosmetics and pharmaceuticals it is used as a pH adjuster and dispersant.

Diethanolamine has also been used to form the soluble salts of active compounds, such as iodinated organic acids that are used as contrast media. As a stabilizing agent, diethanolamine prevents the discoloration of aqueous formulations containing hexamethylenetetramine-1,3-dichloropropene salts.

Diethanolamine is also used in cosmetics.

8 Description

The USPNF 23 describes diethanolamine as a mixture of ethanolamines consisting largely of diethanolamine. At about room temperature it is a white, deliquescent solid. Above room temperature diethanolamine is a clear, viscous liquid with a mildly ammoniacal odor.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for diethanolamine.

Test	USPNF 23
Identification	+
Limit of triethanolamine	⩽1.0%
Organic volatile impurities	+
Refractive index at 30°C	1.473–1.476
Water	⩽0.15%
Assay (anhydrous basis)	98.5–101.0%

10 Typical Properties

Acidity/alkalinity: pH = 11.0 for a 0.1 N aqueous solution.
Autoignition temperature: 662°C
Boiling point: 268.8°C
Density:
1.0881 g/cm^3 at 30°C;
1.0693 g/cm^3 at 60°C.
Dissociation constant: pK_a = 8.88
Flash point (open cup): 138°C
Hygroscopicity: very hygroscopic.
Melting point: 28°C
Refractive index: $n_D^{30} = 1.4753$
Solubility: *see* Table II.

Table II: Solubility of diethanolamine.

Solvent	Solubility at 20°C
Acetone	Miscible
Benzene	1 in 24
Chloroform	Miscible
Ether	1 in 125
Glycerin	Miscible
Methanol	Miscible
Water	1 in 1

Surface tension: 49.0 mN/m (49.0 dynes/cm) at 20°C.
Vapor density (relative): 3.65 (air = 1)
Vapor pressure: >1 Pa at 20°C.
Viscosity (dynamic):
351.9 mPa s (351.9 cP) at 30°C;
53.85 mPa s (53.85 cP) at 60°C.

11 Stability and Storage Conditions

Diethanolamine is hygroscopic and light- and oxygen-sensitive; it should be stored in an airtight container, protected from light, in a cool, dry place.

See Monoethanolamine for further information.

12 Incompatibilities

Diethanolamine is a secondary amine that contains two hydroxy groups. It is capable of undergoing reactions typical of secondary amines and alcohols. The amine group usually exhibits the greater activity whenever it is possible for a reaction to take place at either the amine or a hydroxy group.

Diethanolamine will react with acids, acid anhydrides, acid chlorides, and esters to form amide derivatives, and with propylene carbonate or other cyclic carbonates to give the corresponding carbonates. As a secondary amine, diethanolamine reacts with aldehydes and ketones to yield aldimines and ketimines. Diethanolamine also reacts with copper to form complex salts. Discoloration and precipitation will take place in the presence of salts of heavy metals.

13 Method of Manufacture

Diethanolamine is prepared commercially by the ammonolysis of ethylene oxide. The reaction yields a mixture of monoethanolamine, diethanolamine, and triethanolamine which is separated to obtain the pure products.

14 Safety

Diethanolamine is used in topical and parenteral pharmaceutical formulations, with up to 1.5% w/v being used in intravenous infusions. Experimental studies in dogs have shown that intravenous administration of larger doses of diethanolamine results in sedation, coma, and death.

Animal toxicity studies suggest that diethanolamine is less toxic than monoethanolamine, although in rats the oral acute and subacute toxicity is greater.(1) Diethanolamine is said to be heptacarcinogenic in mice and has also been reported to induce hepatic choline deficiency in mice.(2)

Diethanolamine is an irritant to the skin, eyes, and mucous membranes when used undiluted or in high concentration. However, in rabbits, aqueous solutions containing 10% w/v diethanolamine produce minor irritation. The lethal human oral dose of diethanolamine is estimated to be 5–15 g/kg bodyweight.

The US Cosmetic Ingredient Review Expert Panel evaluated diethanolamine and concluded that it is safe for use in cosmetic formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin. In products intended for prolonged contact with the skin, the concentration of ethanolamines should not exceed 5%. Diethanolamine should not be used in products containing *N*-nitrosating agents.(1) *See also* Section 18.

LD_{50} (guinea pig, oral): 2.0 g/kg(3)
LD_{50} (mouse, IP): 2.3 g/kg
LD_{50} (mouse, oral): 3.3 g/kg
LD_{50} (rabbit, skin): 12.2 g/kg
LD_{50} (rat, IM): 1.5 g/kg
LD_{50} (rat, IP): 0.12 g/kg
LD_{50} (rat, IV): 0.78 g/kg
LD_{50} (rat, oral): 0.71 g/kg
LD_{50} (rat, SC): 2.2 g/kg

15 Handling Precautions

Diethanolamine is irritating to the skin, eyes, and mucous membranes. Protective clothing, gloves, eye protection, and a respirator are recommended. Ideally, diethanolamine should be handled in a fume cupboard. In the UK, the long-term (8-hour TWA) exposure limit for diethanolamine is 13 mg/m^3 (3 ppm).(4) Diethanolamine poses a slight fire hazard when exposed to heat or flame.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IV infusions, ophthalmic solutions, and topical preparations). Included in medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Monoethanolamine; triethanolamine.

18 Comments

Through a standard battery of rodent studies, diethanolamine has been identified by the US National Toxicology Program as a potential carcinogen following topical administration. Several possible confounding issues have been noted during the review of these studies, which may affect the ultimate conclusion made regarding the carcinogenicity of diethanolamine and the relevance of these findings to humans. Diethanolamine is not permitted for use in cosmetics sold within the EU.

19 Specific References

1 Neudahl GA. Diethanolamine (DEA) and diethanolamides toxicology. *Drug Cosmet Ind* 1998; **162**(4): 26–29.
2 Lehman-McKeeman LD, Gamsky EA, Hicks SM, *et al*. Diethanolamine induces hepatic choline deficiency in mice. *Toxicol Sci* 2002; **67**(1): 38–45.
3 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 1235.
4 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.

20 General References

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21 Authors

K Fowler.

22 Date of Revision

17 August 2005.

Diethyl Phthalate

1 Nonproprietary Names

BP: Diethyl phthalate
PhEur: Diethylis phthalas
USPNF: Diethyl phthalate

2 Synonyms

DEP; ethyl benzene-1,2-dicarboxylate; ethyl phthalate; *Kodaflex DEP*; phthalic acid diethyl ester.

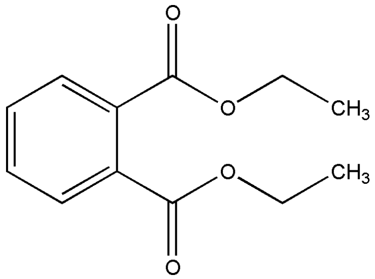
3 Chemical Name and CAS Registry Number

1,2-Benzenedicarboxylic acid, diethyl ester [84-66-2]

4 Empirical Formula and Molecular Weight

$C_{12}H_{14}O_4$ 222.24

5 Structural Formula



6 Functional Category

Film-former; plasticizer; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Diethyl phthalate is used as a plasticizer for film coatings on tablets, beads, and granules at concentrations of 10–30% by weight of polymer.

Diethyl phthalate is also used as an alcohol denaturant and as a solvent for cellulose acetate in the manufacture of varnishes and dopes. In perfumery, diethyl phthalate is used as a perfume fixative at a concentration of 0.1–0.5% of the weight of the perfume used.

8 Description

Diethyl phthalate is a clear, colorless, oily liquid. It is practically odorless, or with a very slight aromatic odor and a bitter, disagreeable taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for diethyl phthalate.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Specific gravity	1.117–1.121	1.118–1.122
Refractive index	1.500–1.505	1.500–1.505
Acidity	+	+
Related substances	+	—
Water	⩽0.2%	⩽0.2%
Residue on ignition	—	⩽0.02%
Sulfated ash	⩽0.1%	—
Assay (anhydrous basis)	99.0–101.0%	98.0–102.0%

10 Typical Properties

Boiling point: 295°C
Flash point: 160°C (open cup)
Melting point: −40°C
Refractive index: $n_D^{25} = 1.501$
Solubility: miscible with ethanol (95%), ether, and many other organic solvents; practically insoluble in water.
Specific gravity: 1.120 at 25°C
Vapor density (relative): 7.66 (air = 1)
Vapor pressure: 1.87 kPa (14 mmHg) at 163°C

11 Stability and Storage Conditions

Diethyl phthalate is stable when stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatible with strong oxidizing materials.

13 Method of Manufacture

Diethyl phthalate is produced by the reaction of phthalic anhydride with ethanol in the presence of sulfuric acid.

14 Safety

Diethyl phthalate is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material at the levels employed as an excipient. However, if consumed in large quantities it can act as a narcotic and cause paralysis of the central nervous system.

Although some animal studies have suggested that high concentrations of diethyl phthalate may be teratogenic, other studies have shown no adverse effects.(1)

LD_{50} (guinea pig, oral): 8.6 g/kg(2)
LD_{50} (mouse, IP): 2.7 g/kg
LD_{50} (mouse, oral): 6.2 g/kg
LD_{50} (rat, IP): 5.1 g/kg
LD_{50} (rat, oral): 8.6 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Diethyl phthalate is irritant to the skin, eyes, and mucous membranes. Protective clothing, eye protection, and nitrile gloves are recommended. Diethyl phthalate should be handled in a fume cupboard or a well-ventilated environment; a respirator is recommended. In the UK, the long-term (8-hour TWA) exposure limit for diethyl phthalate is 5 mg/m^3. The short-term (15-minute) exposure limit is 10 mg/m^3.(3)

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules, delayed action, enteric coated, and sustained action tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Dibutyl phthalate; dimethyl phthalate.

18 Comments

The EINECS number for diethyl phthalate is 201-550-6.

19 Specific References

1 Field EA, Price CJ, Sleet RB, *et al*. Developmental toxicity evaluation of diethyl and dimethyl phthalate in rats. *Teratology* 1993; **48**(1): 33–44.
2 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 1284–1285.
3 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.

20 General References

Banker GS. Film coating theory and practice. *J Pharm Sci* 1966; **55**: 81–89.
Berg JA, Mayor GH. Diethyl phthalate not dangerous [letter]. *Am J Hosp Pharm* 1991; **48**: 1448–1449.
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Chambliss WG. The forgotten dosage form: enteric-coated tablets. *Pharm Technol* 1983; **7**(9): 124, 126, 128, 130, 132, 138.
Health and Safety Executive. Review of the toxicity of the esters of phthalic acid (phthalate esters). *Toxicity Reviews* 14. London: HMSO, 1986.
Kamrin MA, Mayor GH. Diethyl phthalate: a perspective. *J Clin Pharmacol* 1991; **31**: 484–489.
Porter SC, Ridgway K. The permeability of enteric coatings and the dissolution rates of coated tablets. *J Pharm Pharmacol* 1982; **34**: 5–8.
Rowe RC. Materials used in the film coating of oral dosage forms. In: Florence AT, ed. *Materials Used in Pharmaceutical Formulation: Critical Reports on Applied Chemistry*, volume **6**. Oxford: Blackwell Scientific, 1984: 1–36.
Wheatley TA, Steurernagel CR. Latex emulsions for controlled drug delivery. In: McGinity JW, ed. *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*, 2nd edn. New York: Marcel Dekker, 1996: 41–59.

21 Authors

RT Guest.

22 Date of Revision

21 August 2005.

Difluoroethane (HFC)

1 Nonproprietary Names

None adopted.

2 Synonyms

Dymel 152a; ethylene fluoride; *Genetron 152a*; halocarbon 152a; HFC 152a; P-152a; propellant 152a; refrigerant 152a; *Solkane 152a*.

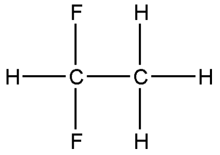
3 Chemical Name and CAS Registry Number

1,1-Difluoroethane [75-37-6]

4 Empirical Formula and Molecular Weight

$C_2H_4F_2$ 66.05

5 Structural Formula



6 Functional Category

Aerosol propellant.

7 Applications in Pharmaceutical Formulation or Technology

Difluoroethane, a hydrofluorocarbon (HFC), is an aerosol propellant used in topical pharmaceutical formulations.(1) Difluoroethane may be used as a vehicle for dispersions and emulsions.

Under the terms of the Montreal Protocol, aimed at reducing damage to the ozone layer, the use of chlorofluorocarbons has been prohibited since January 1996. Since difluoroethane does not contain chlorine, there are no environmental controls on the use of this material as a propellant, since it does not deplete the ozone layer and is not a greenhouse gas.

8 Description

Difluoroethane is a liquefied gas and exists as a liquid at room temperature when contained under its own vapor pressure, or as a gas when exposed to room temperature and atmospheric pressure. The liquid is practically odorless and colorless. Difluoroethane is noncorrosive and nonirritating.

9 Pharmacopeial Specifications

—

10 Typical Properties

Boiling point: −24.7°C
Critical temperature: 113.5°C
Density:
0.90 g/cm^3 for liquid at 25°C;
0.81 g/cm^3 for liquid at 54.5°C.
Flammability: flammable. Limits of flammability 3.7–18.0% v/v in air.
Melting point: −117°C
Solubility: soluble 1 in 357 parts of water at 25°C.
Surface tension: 11.25 mN/m (11.25 dynes/cm) for liquid at 20°C.
Vapor density (absolute): 2.949 g/m^3 at standard temperature and pressure.
Vapor density (relative): 2.29 (air = 1)
Vapor pressure:
600 kPa (61.7 psig) at 21.1°C;
1317 kPa (191 psia) at 54.5°C.
Viscosity (dynamic): 0.243 mPa s (0.243 cP) for liquid at 20°C.

11 Stability and Storage Conditions

Difluoroethane is a nonreactive and stable material. The liquefied gas is stable when used as a propellant and should be stored in a metal cylinder in a cool, dry place.

12 Incompatibilities

Compatible with the usual ingredients used in the formulation of pharmaceutical aerosols.

13 Method of Manufacture

Difluoroethane is prepared from ethyne by the addition of hydrogen fluoride in the presence of a suitable catalyst. The difluoroethane formed is purified to remove all traces of water, as well as traces of the starting materials.

14 Safety

Difluoroethane may be used as an aerosol propellant in topical pharmaceutical formulations. It is generally regarded as an essentially nontoxic and nonirritant material.

Deliberate inhalation of excessive quantities of this propellant may result in death, and the following ‘warning’ statements must appear on the label of all aerosols:

> WARNING: Avoid inhalation. Keep away from eyes or other mucous membranes.

(Aerosols designed specifically for oral and nasal inhalation need not contain this statement.)

> WARNING: Do not inhale directly; deliberate inhalation of contents can cause death.

or

> WARNING: Use only as directed; intentional misuse by deliberately concentrating and inhaling the contents can be harmful or fatal.

Additionally, the label should contain the following information:

> WARNING: Contents under pressure. Do not puncture or incinerate container. Do not expose to heat or store at room temperature above 120°F (49°C). Keep out of the reach of children.

When propellants are used in topical aerosols they may cause a chilling effect on the skin, although this effect has been somewhat overcome by the use of vapor-tap valves. The propellants quickly vaporize from the skin, and are nonirritating when used as directed.

15 Handling Precautions

Difluoroethane is usually encountered as a liquefied gas and appropriate precautions for handling such materials should be taken. Eye protection, gloves, and protective clothing are recommended. Difluoroethane should be handled in a well-ventilated environment. Fluorocarbon vapors are heavier than air and do not support life; therefore, when cleaning large tanks that have contained these propellants, adequate provision for oxygen supply in the tanks must be made in order to protect workers cleaning the tanks.

Difluoroethane is flammable; *see* Section 10. When it is heated to decomposition, toxic fumes of hydrogen fluoride may be formed.

16 Regulatory Status

Accepted in the USA, by the FDA, for use as a topical aerosol propellant.

17 Related Substances

Tetrafluoroethane.

18 Comments

Difluoroethane is useful as an aerosol propellant in that it shows greater miscibility with water than some other fluorocarbons and when combined with chlorodifluoroethane will produce a mixture with a specific gravity of 1. For a discussion of the numerical nomenclature applied to this aerosol propellant, *see* Chlorofluorocarbons.

19 Specific References

1 Sheridan V. Propelling VOCs down. *Manuf Chem* 1995; **66**(10): 57.

20 General References

Johnson MA. *The Aerosol Handbook,* 2nd edn. Caldwell: WE Dorland, 1982: 305–335.

Johnson MA. Flammability aspects of dimethy ether, p-22, p-142b, p-152a. *Aerosol Age* 1988; **33**(8): 32, 34, 36, 38–39.

Sanders PA. *Handbook of Aerosol Technology*, 2nd edn. New York: Van Nostrand Reinhold, 1979: 19–35.

Sciarra JJ. Aerosols. In: Gennaro AR, ed. *Remington: The Science and Practice of Pharmacy*, 19th edn. Easton, PA: Mack Publishing Co., 1995: 1676–1692.

Sciarra JJ. Aerosol suspensions and emulsions. In: Lieberman H, Rieger J, Banker G, eds. *Pharmaceutical Dosage Forms: Disperse Systems*, vol. **2**, 2nd edn. New York: Marcel Dekker, 1996: 319–356.

Sciarra JJ. Pharmaceutical aerosols. In: Banker GS, Rhodes CT, eds. *Modern Pharmaceutics,* 3rd edn. New York: Marcel Dekker, 1996: 547–574.

Sciarra JJ, Stoller L. *The Science and Technology of Aerosol Packaging*. New York: Wiley, 1974: 137–145.

21 Authors

CJ Sciarra, JJ Sciarra.

22 Date of Revision

23 August 2005.

Dimethicone

1 Nonproprietary Names

BP: Dimeticone
PhEur: Dimeticonum
USPNF: Dimethicone

2 Synonyms

ABIL; dimethylpolysiloxane; dimethylsilicone fluid; dimethylsiloxane; *Dow Corning Q7-9120*; E900; methyl polysiloxane; poly(dimethylsiloxane); *Sentry*.

3 Chemical Name and CAS Registry Number

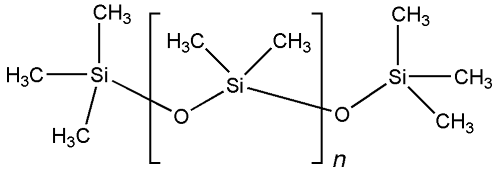
α-(Trimethylsilyl)-ω-methylpoly[oxy(dimethylsilylene)] [9006-65-9]

4 Empirical Formula and Molecular Weight

The PhEur 2005 describes dimethicone as a polydimethylsiloxane obtained by hydrolysis and polycondensation of dichlorodimethylsilane and chlorotrimethylsilane. The degree of polymerization (n = 20–400) is such that materials with kinematic viscosities nominally 20–1300 mm^2/s (20–1300 cSt) are produced. Dimethicones with a nominal viscosity of 50 mm^2/s (50 cSt) or lower are intended for external use only.

The USPNF 23 describes dimethicone as a mixture of fully methylated linear siloxane polymers containing repeating units of the formula $[-(CH_3)_2SiO-]_n$ stabilized with trimethylsiloxy end-blocking units of the formula $[(CH_3)_3SiO-]$, where n has an average value such that the corresponding nominal viscosity is in a discrete range 20–30 000 mm^2/s (20–30 000 cSt).

5 Structural Formula



6 Functional Category

Antifoaming agent; emollient.

7 Applications in Pharmaceutical Formulation or Technology

Dimethicones of various viscosities are widely used in cosmetic and pharmaceutical formulations. In topical oil-in-water emulsions dimethicone is added to the oil phase as an antifoaming agent. Dimethicone is hydrophobic and is also widely used in topical barrier preparations. Therapeutically, dimethicone may be used with simethicone in oral pharmaceutical formulations used in the treatment of flatulence. Dimethicone is also used to form a water-repellent film on glass containers. *See* Table I.

Table I: Uses of dimethicone.

Use	Concentration (%)
Creams, lotions and ointments	10–30
Oil–water emulsions	0.5–5.0

8 Description

Dimethicones are clear, colorless liquids available in various viscosities; *see* Section 4.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for dimethicone.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Acidity	+	+
Specific gravity	—	+[a]
Viscosity (kinematic) of the nominal stated value	90–110%	+[a]
Refractive index	—	+[a]
Mineral oils	+	—
Phenylated compounds	+	—
Heavy metals	⩽5 ppm	⩽5 μg/g
Volatile matter (for dimethicones with a viscosity greater than 50 mm^2/s (50 cSt)	⩽0.3%	—
Loss on heating	—	+[a]
Bacterial endotoxins (coating of containers for parenteral use)	—	+
Assay (of polydimethylsiloxane)	—	97.0–103.0%

[a] The USPNF 23 specifies limits for these tests specific to the nominal viscosity of the dimethicone.

10 Typical Properties

Acid value: <0.01
Density: 0.94–0.98 g/cm^3 at 25°C
Refractive index: n_D^{25} = 1.401–1.405
Solubility: miscible with ethyl acetate, methyl ethyl ketone, mineral oil, and toluene; soluble in isopropyl myristate, very slightly soluble in ethanol (95%); practically insoluble in glycerin, propylene glycol, and water.
Surface tension: 20.5–21.2 mN/m at 25°C

11 Stability and Storage Conditions

Dimethicones should be stored in an airtight container in a cool, dry, place; they are stable to heat and are resistant to most chemical substances although they are affected by strong acids. Thin films of dimethicone may be sterilized by dry heat for at least 2 hours at 160°C. Sterilization of large quantities of dimethicone by steam autoclaving is not recommended since excess water diffuses into the fluid causing it to become hazy. However, thin films may be sterilized by this method. Gamma irradiation may also be used to sterilize dimethicone. Gamma irradiation can, however, cause cross-linking with a consequent increase in the viscosity of fluids.

12 Incompatibilities

—

13 Method of Manufacture

Dimethicone is a poly(dimethylsiloxane) obtained by hydrolysis and polycondensation of dichlorodimethylsilane and chlorotrimethylsilane. The hydrolysis products contain active silanol groups through which condensation polymerization proceeds. By varying the proportions of chlorotrimethylsilane, which acts as a chain terminator, silicones of varying molecular weight may be prepared. Different grades of dimethicone are produced that may be distinguished by a number placed after the name indicating the nominal viscosity. For example, *ABIL 20* (Goldschmidt UK Ltd) has a nominal kinematic viscosity of 18–22 mm^2/s (18–22 cSt). *See also* Section 4.

14 Safety

Dimethicone is generally regarded as a relatively nontoxic and nonirritant material although it can cause temporary irritation to the eyes. In pharmaceutical formulations it may be used in oral and topical preparations. Dimethicones are also used extensively in cosmetic formulations and in certain food applications.

The WHO has set a tentative estimated acceptable daily intake of dimethicone with a relative molecular mass in the range of 200–300 at up to 1.5 mg/kg body-weight.(1)

Injection of silicones into tissues may cause granulomatous reactions. Accidental intravascular injection has been associated with fatalities.

LD_{50} (mouse, oral): >20 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Dimethicone is flammable and should not be exposed to naked flames or heat.

16 Regulatory Status

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets, topical creams, emulsions, lotions, and transdermal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Cyclomethicone; simethicone.

18 Comments

—

19 Specific References

1 FAO/WHO. Evaluation of certain food additives. Twenty-third report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1980; No. 648.

20 General References

Calogero AV. Regulatory review. *Cosmet Toilet* 2000; **115**(May): 24, 26, 27.

21 Authors

RT Guest.

22 Date of Revision

21 August 2005.

Dimethyl Ether

1 Nonproprietary Names

None adopted.

2 Synonyms

Dimethyl oxide; DME; *Dymel A*; methoxymethane; methyl ether; oxybismethane; wood ether.

3 Chemical Name and CAS Registry Number

Dimethyl ether [115-10-6]

4 Empirical Formula and Molecular Weight

C_2H_6O 46.07

5 Structural Formula

$$H_3C-O-CH_3$$

6 Functional Category

Aerosol propellant.

7 Applications in Pharmaceutical Formulation or Technology

Dimethyl ether may be used as an aerosol propellant for topical aerosol formulations in combination with hydrocarbons and other propellants.(1–4) Generally, it cannot be used alone as a propellant owing to its high vapor pressure. Dimethyl ether is a good solvent and has the unique property of high water solubility, compared to other propellants. It has frequently been used with aqueous aerosols. A coarse, wet, spray is formed when dimethyl ether is used as a propellant.

Dimethyl ether is also used as a propellant in cosmetics such as hair sprays, and in other aerosol products such as air fresheners and fly sprays.

Dimethyl ether is additionally used as a refrigerant.

8 Description

Dimethyl ether is a liquefied gas and exists as a liquid at room temperature when contained under its own vapor pressure, or as a gas when exposed to room temperature and pressure.

It is a clear, colorless, virtually odorless liquid. In high concentrations, the gas has a faint etherlike odor.

9 Pharmacopeial Specifications

—

10 Typical Properties

Autoignition temperature: 350°C
Boiling point: −23.6°C
Critical temperature: 126.9°C
Density: 0.66 g/cm^3 for liquid at 25°C.
Flammability: the pure material is flammable; limit of flammability is 3.4–18.2% v/v in air. Aqueous mixtures are nonflammable.
Freezing point: −138.5°C
Flash point: −41°C
Heat of combustion: −28.9 kJ/g (−6900 cal/g)
Kauri-butanol value: 60
Solubility: soluble in acetone, chloroform, ethanol (95%), ether, and 1 in 3 parts of water. Dimethyl ether is generally miscible with water, nonpolar materials, and some semipolar materials. For pharmaceutical aerosols, ethanol (95%) is the most useful cosolvent. Glycols, oils, and other similar materials exhibit varying degrees of miscibility with dimethyl ether.
Surface tension: 16 mN/m (16 dynes/cm) at −10°C
Vapor density (absolute): 2.058 g/m^3 at standard temperature and pressure.
Vapor density (relative): 1.596 (air = 1)
Vapor pressure:
592 kPa at 25°C (63 psig at 21.1°C);
1301 kPa at 54°C.

11 Stability and Storage Conditions

The liquefied gas is stable when used as a propellant. However, exposure to the air for long periods of time may result in explosive peroxides being slowly formed.

Solutions of liquid dimethyl ether should not be concentrated either by distillation or by evaporation. Dimethyl ether should be stored in tightly closed metal cylinders in a cool, dry place.

12 Incompatibilities

Dimethyl ether is an aggressive solvent and may affect the gasket materials used in aerosol packaging. Oxidizing agents, acetic acid, organic acids, and anhydrides should not be used with dimethyl ether. *See also* Section 10.

13 Method of Manufacture

Dimethyl ether is prepared by the reaction of bituminous or lignite coals with steam in the presence of a finely divided nickel catalyst. This reaction produces formaldehyde, which is then reduced to methanol and dimethyl ether. Dimethyl ether may also be prepared by the dehydration of methanol.

14 Safety

Dimethyl ether may be used as a propellant and solvent in topical pharmaceutical aerosols, and is generally regarded as an essentially nontoxic and nonirritant material when used in such applications. However, inhalation of high concentrations of dimethyl ether vapor is harmful. Additionally, skin contact with dimethyl ether liquid may result in freezing of the skin and severe frostbite.

When used in topical formulations, dimethyl ether may exert a chilling effect on the skin, although if it is used as directed the propellant quickly vaporizes and is nonirritating.

LD_{50} (mouse, inhalation): 386 000 ppm/30 min(5)
LD_{50} (rat, inhalation): 308 g/m^3

15 Handling Precautions

Dimethyl ether is usually encountered as a liquefied gas, and appropriate precautions for handling such materials should be taken. Eye protection, gloves, and protective clothing are recommended.

Dimethyl ether should be handled in a well-ventilated environment.

Dimethyl ether vapor is heavier than air and does not support life; therefore, when cleaning large tanks that have contained this material, adequate provisions for oxygen supply in the tanks must be made in order to protect workers cleaning the tanks.

In the UK, the long-term (8-hour TWA) exposure limit for dimethyl ether is 766 mg/m^3 (400 ppm). The short-term (15-minute) exposure limit is 958 mg/m^3 (500 ppm).(6)

Dimethyl ether is flammable; *see* Section 10.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (topical aerosols). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Hydrocarbons (HC).

18 Comments

Since the solubility of dimethyl ether in water is about 35%, it can be used to good effect in aqueous aerosol products. It also has antimicrobial effects that are organism-dependent.(7)

The EINECS number for dimethyl ether is 204-065-8.

19 Specific References

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21 Authors

CJ Sciarra, JJ Sciarra.

22 Date of Revision

23 August 2005.

Dimethyl Phthalate

1 Nonproprietary Names

BP: Dimethyl phthalate

2 Synonyms

Avolin; 1,2-benzenedicarboxylate; benzenedicarboxylic acid dimethyl ester; dimethyl 1,2-benzenedicarboxylate; dimethyl benzene-*o*-dicarboxylate; dimethyl benzeneorthodicarboxylate; dimethyl *o*-phthalate; *o*-dimethyl phthalate; DMP; *Fermine*; *Kodaflex DMP*; methyl benzene-1,2-dicarboxylate; *Mipax*; *Palatinol M*; phthalic acid dimethyl ester; phthalic acid methyl ester; *Repeftal*; *Solvanom*; *Solvarone*; *Unimoll DM*.

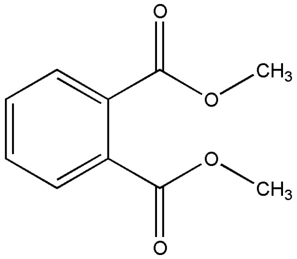
3 Chemical Name and CAS Registry Number

1,2-Benzene-dicarboxylic acid dimethyl ester [131-11-3]

4 Empirical Formula and Molecular Weight

$C_{10}H_{10}O_4$ 194.19

5 Structural Formula



6 Functional Category

Film-former; plasticizer; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Dimethyl phthalate is used in pharmaceutical applications as a solvent and plasticizer for film-coatings such as hydroxypropyl methylcellulose, cellulose acetate and cellulose acetate–butyrate mixtures.(1,2)

In addition to a number of industrial applications, dimethyl phthalate is also widely used as an insect repellent with topical preparations typically applied as a 40% cream or lotion; it has also been applied as a tent fabric treatment.(3)

8 Description

Dimethyl phthalate occurs as a colorless, or faintly colored, odorless, viscous, oily liquid.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for dimethyl phthalate.

Test	BP 2004
Identification	+
Characters	+
Acidity	+
Refractive index	1.515–1.517
Weight per mL	1.186–1.192
Related substances	+
Sulfated ash	⩽0.1%
Water	⩽0.1%
Assay (dried basis)	99.0–100.5%

10 Typical Properties

Boiling point: 280°C, with decomposition.
Density: 1.186–1.192 g/cm³
Flash point: 146°C closed cup.
Freezing point: the commercial product freezes at 0°C.
Melting point: 2.0–5.5°C
Partition coefficient:
Octanol : water = 1.56(4)
Refractive index: n_D^{20} = 1.515–1.517
Solubility: *see* Table II.

Table II: Solubility of dimethyl phthalate.

Solvent	Solubility at 20°C unless otherwise stated
Benzene	Miscible
Chloroform	Miscible
Ethanol (95%)	Miscible
Ether	Miscible
Mineral oil	1 in 294
Water	1 in 250 at 20°C

Surface tension: 41.9 mN/m at 20°C
Vapor density (relative): 6.69 (air = 1)
Vapor pressure: 120 Pa at 100°C
Viscosity: 17.2 mPa s (17.2 cP) at 25°C.

11 Stability and Storage Conditions

Dimethyl phthalate is sensitive to prolonged exposure to light and it should therefore be stored in a cool, dark, dry, well-ventilated area that is protected from physical damage, and isolated from incompatible substances. Containers of dimethyl phthalate may be hazardous when empty as they may retain product residues such as vapors and liquids. There is a slight fire hazard when exposed to heat, and above the flash point (*see* Section 10); explosive vapor–air mixtures may be formed. Carbon dioxide and carbon monoxide are released when dimethyl phthalate is heated to decomposition. Solutions of dimethyl phthalate in acetone, dimethyl sulfoxide, ethanol

(95%), and water are stable for 24 hours under normal laboratory conditions.

12 Incompatibilities

Dimethyl phthalate is incompatible with strong acids or bases, nitrates, and strong oxidizing agents.

13 Method of Manufacture

Dimethyl phthalate is produced industrially from phthalic anhydride and methanol.

14 Safety

In pharmaceutical applications, dimethyl phthalate is used in film-coating and as a topically applied insect repellent. Acute exposure to the eyes and mucous membranes can cause irritation although dimethyl phthalate is considered less irritant than diethyl phthalate. Inhalation of dimethyl phthalate can cause irritation of the respiratory tract; oral ingestion can cause a burning sensation in the mouth, vomiting, and diarrhea. Owing to the low water solubility and relatively high lipid solubility, dimethyl phthalate may accumulate in body tissues after chronic exposure, which may cause central nervous system depression.

Although some animal studies have suggested that high concentrations of dimethyl phthalate may be teratogenic or cause mutagenic effects with bacteria,(5,6) other studies have shown no adverse effects.(7) There are no confirmed reports of human reproductive or developmental effects and the compound is not generally regarded as a carcinogenic material.

LD_{50} (chicken, oral): 8.5 g/kg(8)
LD_{50} (guinea pig, oral): 2.4 g/kg
LD_{50} (mouse, IP): 1.38 g/kg
LD_{50} (mouse, oral): 6.8 g/kg
LD_{50} (rabbit, oral): 4.40 g/kg
LD_{50} (rat, IP): 3.38 g/kg
LD_{50} (rat, oral): 6.80 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Skin and eye contact should be avoided; eye goggles or a full face shield should be worn where splashing may occur. Respirators should be used if the compound is heated to decomposition. In the UK, the long-term (8-hour TWA) exposure limit for dimethyl phthalate is 5 mg/m^3. The short-term (15-minute) exposure limit is 10 mg/m^3.(9)

16 Regulatory Status

Dimethyl phthalate is included in a number of topical pharmaceutical formulations. As from 1992, dimethyl phthalate is no longer registered for use as a pesticide in California.

17 Related Substances

Dibutyl phthalate; diethyl phthalate.

18 Comments

The EINECS number for dimethyl phthalate is 205-011-6.

19 Specific References

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20 General References

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21 Authors

W Cook.

22 Date of Revision

4 August 2005.

Dimethyl Sulfoxide

1 Nonproprietary Names

BP: Dimethyl sulfoxide
PhEur: Dimethylis sulfoxidum
USP: Dimethyl sulfoxide

2 Synonyms

Deltan; dimexide; dimethyl sulphoxide; DMSO; *Kemsol*; methylsulfoxide; *Rimso-50*; sulphinylbismethane

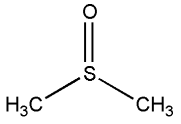
3 Chemical Name and CAS Registry Number

Sulfinylbismethane [67-68-5]

4 Empirical Formula and Molecular Weight

C_2H_6OS 78.13

5 Structural Formula



6 Functional Category

Penetration enhancer; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Dimethyl sulfoxide is a highly polar substance that is aprotic, therefore lacking acidic and basic properties. It has exceptional solvent properties for both organic and inorganic components, which are derived from its capacity to associate with both ionic species and neutral molecules that are either polar or polarizable. Dimethyl sulfoxide enhances the topical penetration of drugs owing to its ability to displace bound water from the stratum corneum; this is accompanied by the extraction of lipids and configurational changes of proteins.(1) The molecular interactions between dimethyl sulfoxide and the stratum corneum, as a function of depth and time, have been described.(2) Much of the enhancement capacity is lost if the solvent is diluted. Increases in drug penetration have been reported with dimethyl sulfoxide concentrations as low as 15%, but significant increases in permeability generally require concentrations higher than 60–80%. Furthermore, while low molecular weight substances can penetrate quickly into the deep layers of the skin, the appreciable transport of molecules with a molecular weight of more than 3000 is difficult.

The use of dimethyl sulfoxide to improve transdermal delivery has been reported for ciclosporin,(3) timolol,(4) and a wide range of other drugs.(5,6) Dimethyl sulfoxide has also been used in the formulation of an injection containing allopurinol.(7) It has also been investigated for use in an experimental parenteral preparation for the treatment of liver tumors.(8)

In paint formulations of idoxuridine, dimethyl sulfoxide acts both as a solvent to increase drug solubility and a means of enabling penetration of the antiviral agent to the deeper levels of the epidermis. *See* Table I.

Dimethyl sulfoxide has also been investigated as a potential therapeutic agent in conditions such as scleroderma, interstitial cystitis, rheumatoid arthritis, and acute musculoskeletal injuries, and as an analgesic.(9–13) It has also been recommended for the treatment of anthracycline extravasation(14,15) and has been investigated as a potential cryoprotectant.(16)

Table I: Uses of dimethyl sulfoxide.

Use	Concentration (%)
Solvent	⩽100
Topical penetration enhancer	⩾80

8 Description

Dimethyl sulfoxide occurs as a colorless, viscous liquid, or as colorless crystals that are miscible with water, alcohol, and ether. The material has a slightly bitter taste with a sweet aftertaste and is odorless, or has a slight odor characteristic of dimethyl sulfoxide. Dimethyl sulfoxide is extremely hygroscopic, absorbing up to 70% of its own weight in water with evolution of heat.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for dimethyl sulfoxide.

Test	PhEur 2005	USP 28
Characters	+	—
Identification	+	+
Specific gravity	1.100–1.104	1.095–1.101
Freezing point	⩾18.3°C	⩾18.3°C
Refractive index	1.478–1.479	1.4755–1.4775
Acidity	+	+
Water	⩽0.2%	⩽0.1%
Ultraviolet absorbance	+	+
Substances darkened by potassium hydroxide	—	+
Limit of dimethyl sulfone	—	+
Limit of nonvolatile residue	—	⩽5.0 mg
Related substances	+	—
Assay	—	⩾99.9%

10 Typical Properties

Boiling point: 189°C
Dielectric constant: 48.9 at 20°C
Dipole moment (*D*): 4.3 at 20°C(17)
Dissociation constant: $pK_a = 31.3$(17)
Enthalpy of fusion: 3.43 cal/mol(17)

Enthalpy of vaporization: 12.64 cal/mol at 25°C(17)
Flash point (open cup): 95°C
Specific heat: 0.7 cal/g (liquid)
Solubility: miscible with water with evolution of heat; also miscible with ethanol (95%), ether and most organic solvents; immiscible with paraffins, hydrocarbons. Practically insoluble in acetone, chloroform, ethanol (95%), and ether.
Vapor pressure: 0.37 mm at 20°C
Viscosity (dynamic): 1.1 mPa s (1.1 cP) at 27°C

11 Stability and Storage Conditions

Dimethyl sulfoxide is reasonably stable to heat but upon prolonged reflux it decomposes slightly to methyl mercaptan and bismethylthiomethane. This decomposition is aided by acids, and is retarded by many bases. When heated to decomposition, toxic fumes are emitted.

At temperatures between 40–60°C, it has been reported that dimethyl sulfoxide suffers a partial breakdown, which is indicated by changes in physical properties such as refractive index, density, and viscosity.(18)

Dimethyl sulfoxide should be stored in airtight, light-resistant containers. The PhEur 2005 states that glass containers should be used. Contact with plastics should be avoided.

12 Incompatibilities

Dimethyl sulfoxide can react with oxidizing materials.

13 Method of Manufacture

Dimethyl sulfoxide is prepared by air oxidation of dimethyl sulfide in the presence of nitrogen oxides. It can also be obtained as a by-product of wood pulp manufacture for the paper and allied industries.

14 Safety

Dimethyl sulfoxide has low systemic toxicity but causes local toxic effects.(19–21) It is readily absorbed after injection or after oral or percutaneous administration and is widely distributed throughout the body. Dimethyl sulfoxide acts as a primary irritant on skin, causing redness, burning, itching, and scaling; it also causes urticaria. Systemic symptoms include nausea, vomiting, chills, cramps, and lethargy; dimethyl sulfoxide can also cause increases in intraocular pressure. Administration of dimethyl sulfoxide by any route is followed by a garlic-like odor on the breath.

Intravascular hemolysis and biochemical changes(22) and reversible neurological deterioration(23) have been reported following intravenous administration; however, it has been questioned whether these findings were directly attributable to dimethyl sulfoxide rather than to concomitant drug therapy or contaminants.(24) Recently, a hypersensitivity reaction attributed to dimethyl sulfoxide has been reported.(25)

In 1965, the FDA banned investigation in humans of dimethyl sulfoxide owing to the appearance of changes in the refractive index of the lens of the eye in experimental animals. However, in 1966, the FDA allowed the study of dimethyl sulfoxide in serious conditions such as scleroderma, persistent herpes zoster, and severe rheumatoid arthritis, and in 1968 permitted studies using short-term topical application of the solvent. By 1980, the FDA no longer specifically regulated investigations of dimethyl sulfoxide.(10)

Dimethyl sulfoxide enhances the skin penetration of several drugs, which may result in producing the adverse effects associated with those drugs.

LD_{50} (dog, IV): 2.5 g/kg(26)
LD_{50} (rat, IP): 8.2 g/kg
LD_{50} (rat, IV): 5.3 g/kg
LD_{50} (rat, oral): 14.5 g/kg
LD_{50} (rat, SC): 12 g/kg
LD_{50} (mouse, IP): 2.5 g/kg
LD_{50} (mouse, IV): 3.8 g/kg
LD_{50} (mouse, oral): 7.9 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Dimethyl sulfoxide may cause irritation to the skin. Gloves and eye protection are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IV infusions, SC implants, and topical preparations). Available in the USA as a 50% solution for irrigation in the treatment of interstitial cystitis. Also available in Canada as a 70% solution for use as a topical antifibrotic and in Germany as a topical gel containing 10% dimethyl sulfoxide for the treatment of musculoskeletal and joint disorders. Included in topical formulations of idoxuridine and diclofenac licensed in the UK.

17 Related Substances

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18 Comments

A 2.16% dimethyl sulfoxide solution in water is iso-osmotic with serum. Dimethyl sulfoxide has been used as a 50% aqueous solution for instillation into the bladder in the treatment of interstitial cystitis; it has also been tried clinically for a wide range of indications, including cutaneous and musculoskeletal disorders, but with little evidence of beneficial effects.

Dimethyl sulfoxide has been shown to have bactericidal,(27) bacteriostatic,(27,28) and fungistatic(28) activity, although the concentration required is dependent on the organism present.

19 Specific References

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21 Authors

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22 Date of Revision

19 August 2005.

Dimethylacetamide

1 Nonproprietary Names

BP: Dimethylacetamide
PhEur: Dimethylacetamidum

2 Synonyms

Acetdimethylamide; acetic acid dimethylamide; acetyldimethylamine; dimethylacetone amide; dimethylamide acetate; DMA; DMAC.

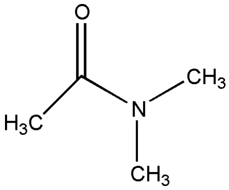
3 Chemical Name and CAS Registry Number

N,*N*-Dimethylacetamide [127-19-5]

4 Empirical Formula and Molecular Weight

C_4H_9NO 87.12

5 Structural Formula



6 Functional Category

Solvent.

7 Applications in Pharmaceutical Formulation or Technology

Dimethylacetamide is used as a solvent in oral and injectable pharmaceutical formulations.(1) It has been used as a cosolvent to solubilize poorly soluble drugs.(2–4) The use of dimethylacetamide has also been investigated as a vehicle for the parenteral delivery of relatively small peptides.(5)

The use of solvents such as dimethylacetamide has been shown to influence the size and rate of release of norfloxacin from nanoparticles.(6)

Dimethylacetamide has also been used in topical formulations and has been evaluated as a permeation enhancer for transdermal drug delivery.(1)

8 Description

Dimethylacetamide occurs as a clear, colorless, slightly hygroscopic liquid. It has a weak ammonia-like or fishlike odor.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for dimethylacetamide.

Test	PhEur 2005 (Suppl. 5.1)
Identification	+
Characters	+
Appearance	+
Relative density	0.941–0.944
Refractive index	1.435–1.439
Acidity	+
Alkalinity	+
Related substances	+
Heavy metals	⩽10 ppm
Nonvolatile matter	⩽20 ppm
Water	⩽0.1%

10 Typical Properties

Autoignition temperature: 490°C
Boiling point: 165°C
Dielectric constant: $D^{20} = 37.8$
Flash point: 70°C
Refractive index: $n_D^{22.5} = 1.4371$
Solubility: miscible with ethanol (95%), water, and most common solvents.
Specific gravity: 0.943
Surface tension: 35.7 mN/m (35.7 dyne/cm)
Vapor pressure: 0.33 kPa at 20°C
Viscosity (dynamic): 1.02 mPa s (1.02 cP) at 25°C

11 Stability and Storage Conditions

Dimethylacetamide should be stored in an airtight container, protected from light, in a cool, dry, place. Dimethylacetamide has an almost unlimited shelf-life when kept in closed containers and under nitrogen. It is combustible.

12 Incompatibilities

Dimethylacetamide is incompatible with carbon tetrachloride, oxidizing agents, halogenated compounds, and iron. It attacks plastic and rubber. Contact with strong oxidizers may cause fire.

13 Method of Manufacture

Dimethylacetamide is manufactured from acetic acid and dimethylamine in a closed system.

14 Safety

Dimethylacetamide is used in pharmaceutical preparations as a solvent in parenteral formulations and is generally regarded as a nontoxic material when used as an excipient. Animal toxicity studies indicate that dimethylacetamide is readily absorbed into the bloodstream following inhalation or topical application. Repeated exposure to dimethylacetamide may be harmful and can result in liver damage. High intravenous doses (>400 mg/kg/day for 3 days) may be hallucinogenic.(7–10)

LD_{50} (rabbit, SC): 9.6 g/kg(11)
LD_{50} (rat, IP): 2.75 g/kg
LD_{50} (rat, IV): 2.64 g/kg
LD_{50} (rat, oral): 4.93 g/kg
LD_{50} (mouse, inhalation): 7.2 g/kg
LD_{50} (mouse, IP): 2.8 g/kg
LD_{50} (mouse, IV): 3.02 g/kg
LD_{50} (mouse, SC): 9.6 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled. Dimethylacetamide can be absorbed into the bloodstream by inhalation and through the skin; it is irritating to the skin and eyes.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IM injections, IV injections and infusions). Included in parenteral medicines licensed in the UK.

17 Related Substances

—

18 Comments

The EINECS number for dimethylacetamide is 204-826-4. A specification for dimethylacetamide is included in the Japanese Pharmaceutical Excipients (JPE) 2004.(12)

19 Specific References

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21 Authors

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22 Date of Revision

21 August 2005.

Disodium Edetate

1 Nonproprietary Names

BP: Disodium edetate
JP: Disodium edetate
PhEur: Dinatrii edetas
USP: Edetate disodium

2 Synonyms

Disodium EDTA; disodium ethylenediaminetetraacetate; edathamil disodium; edetate disodium; edetic acid, disodium salt.

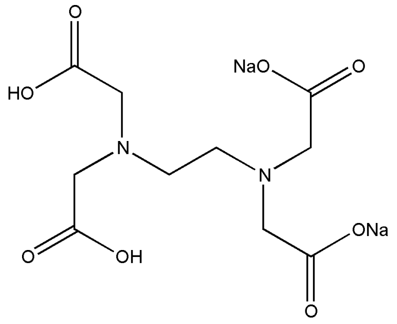
3 Chemical Name and CAS Registry Number

Ethylenediaminetetraacetic acid, disodium salt [139-33-3]
Disodium ethylenediaminetetraacetate dihydrate [6381-92-6]

4 Empirical Formula and Molecular Weight

$C_{10}H_{14}N_2Na_2O_8$	336.2 (for anhydrous)
$C_{10}H_{18}N_2Na_2O_{10}$	372.2 (for dihydrate)

5 Structural Formula



6 Functional Category

Chelating agent.

7 Applications in Pharmaceutical Formulation or Technology

Disodium edetate is used as a chelating agent in a wide range of pharmaceutical preparations, including mouthwashes, ophthalmic preparations, and topical preparations,(1–3) typically at concentrations between 0.005 and 0.1% w/v.

Disodium edetate forms stable water-soluble complexes (chelates) with alkaline earth and heavy-metal ions. The chelated form has few of the properties of the free ion, and for this reason chelating agents are often described as 'removing' ions from solution, a process known as sequestering. The stability of the metal–edetate complex is dependent on the metal ion involved and the pH.

Disodium edetate is also used as a water softener as it will chelate calcium and magnesium ions present in hard water. It is also used therapeutically as an anticoagulant as it will chelate calcium and prevent the coagulation of blood *in vitro*. Concentrations of 0.1% w/v are used in small volumes for hematological testing and 0.3% w/v in transfusions.

See also Edetic acid.

8 Description

Disodium edetate occurs as a white crystalline, odorless powder with a slightly acidic taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for disodium edetate.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	+	+	—
Appearance of solution	+	+	—
pH	4.3–4.7	4.0–5.5	4.0–6.0
Iron	—	⩽80 ppm	—
Calcium	—	—	+
Heavy metals	⩽10 ppm	⩽20 ppm	⩽0.005%
Cyanide	+	—	—
Arsenic	⩽2 ppm	—	—
Limit of nitrilotriacetic acid	—	⩽0.1%	⩽0.1%
Residue on ignition	37.0–39.0%	—	—
Loss on drying	—	—	8.7–11.4%
Assay	98.5–101.0%	98.5–101.0%	99.0–101.0%

10 Typical Properties

Acidity/alkalinity: pH 4.3–4.7 (1% w/v solution in carbon dioxide-free water)
Freezing point depression: 0.14°C (1% w/v aqueous solution)
Melting point: decomposition at 252°C for the dihydrate.
Refractive index: 1.33 (1% w/v aqueous solution)
Solubility: practically insoluble in chloroform and ether; slightly soluble in ethanol (95%); soluble 1 part in 11 parts water.
Specific gravity: 1.004 (1% w/v aqueous solution)
Viscosity (kinematic): 1.03 mm^2/s (1.03 cSt) (1% w/v aqueous solution).

11 Stability and Storage Conditions

Edetate salts are more stable than edetic acid (*see also* Edetic acid). However, disodium edetate dihydrate loses water of crystallization when heated to 120°C. Aqueous solutions of disodium edetate may be sterilized by autoclaving, and should be stored in an alkali-free container.

Disodium edetate is hygroscopic and is unstable when exposed to moisture. It should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Disosium edetate behaves as a weak acid, displacing carbon dioxide from carbonates and reacting with metals to form hydrogen. It is incompatible with strong oxidizing agents, strong bases, metal ions, and metal alloys.

See also Edetic acid.

13 Method of Manufacture

Disodium edetate may be prepared by the reaction of edetic acid and sodium hydroxide.

14 Safety

Disodium edetate is used widely in topical, oral, and parenteral pharmaceutical formulations; it is used extensively in cosmetic and food products. Disodium edetate and edetate calcium disodium are used in a greater number and variety of pharmaceutical formulations than is edetic acid. Both disodium edetate and edetate calcium disodium are poorly absorbed from the gastrointestinal tract and are associated with few adverse effects when used as excipients in pharmaceutical formulations.

Disodium edetate, trisodium edetate, and edetic acid readily chelate calcium and can, in large doses, cause calcium depletion (hypocalcemia) if used over an extended period of time, or if administered too rapidly by intravenous infusion. If used in preparations for the mouth, they can also leach calcium from the teeth. However, edetate calcium disodium does not chelate calcium.

Disodium edetate should be used with caution in patients with renal impairment, tuberculosis, and impaired cardiac function.

Although disodium edetate is generally considered safe, there have been reports of disodium edetate toxicity in patients receiving chelation therapy.(4)

Nasal formulations containing benzalkonium chloride and disodium edetate, both known to be local irritants, were shown to produce an inflammatory reaction, and microscopic examination showed an extended infiltration of the mucosa by eosinophils, and pronounced atrophy and disorganization of the epithelium, although these effects were subsequently shown to be reversible.(3)

The WHO has set an estimated acceptable daily intake for disodium EDTA in foodstuffs of up to 2.5 mg/kg body-weight.(5) *See also* Edetic acid.

LD_{50} (mouse, IP): 0.26 g/kg(6)
LD_{50} (mouse, IV): 0.056 g/kg
LD_{50} (mouse, OP): 2.05 g/kg
LD_{50} (rabbit, IV): 0.047 g/kg
LD_{50} (rabbit, OP): 2.3 g/kg
LD_{50} (rat, OP): 2.0 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Disodium edetate and its derivatives are mild irritants to the mucous membranes. Eye protection, gloves, and dust masks are recommended.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (inhalations; injections; ophthalmic preparations; oral capsules, solutions, suspensions, syrups, and tablets; rectal topical, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Edetic acid.

18 Comments

Disodium edetate has been used experimentally to investigate the stability and skin penetration capacity of captopril gel, in which disodium edetate was shown to exert a potent stabilizing effect, and may be used in the development of a transdermal drug delivery system.(7)

A chitosan–EDTA conjugate has been investigated as a novel polymer for use in topical gels. The conjugate was shown to be stable, colorless, and transparent, and it also demonstrated antimicrobial effects.(8)

The EINECS number for disodium edetate is 205-358-3.

19 Specific References

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2 Kaur IP, Singh M, Kanwar M. Formulation and evaluation of ophthalmic preparations of acetazolamide. *Int J Pharm* 2000; **199**: 119–127.
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5 FAO/WHO. Toxicological evaluation of certain food additives with a review of general principles and of specifications. Seventeenth report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1974; No. 539.
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8 Valenta C, Christen B, Bernkop-Schnurch A. Chitosan–EDTA conjugate: novel polymer for topical gels. *J Pharm Pharmacol* 1998; **50**: 445–452.

20 General References

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21 Authors

S Shah, D Thassu.

22 Date of Revision

15 August 2005.

Docusate Sodium

1 Nonproprietary Names

BP: Docusate sodium
PhEur: Docusatum natricum
USP: Docusate sodium

2 Synonyms

Bis(2-ethylhexyl) sodium sulfosuccinate; dioctyl sodium sulfosuccinate; DSS; sodium dioctyl sulfosuccinate; sulfo-butanedioic acid 1,4-bis(2-ethylhexyl) ester, sodium salt.

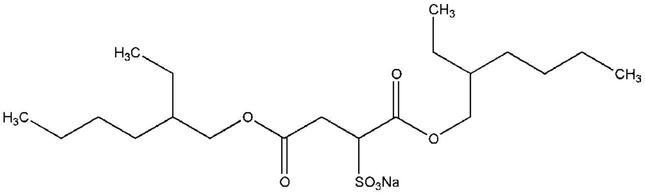
3 Chemical Name and CAS Registry Number

Sodium 1,4-bis(2-ethylhexyl) sulfosuccinate [577-11-7]

4 Empirical Formula and Molecular Weight

$C_{20}H_{37}NaO_7S$ 444.56

5 Structural Formula



6 Functional Category

Anionic surfactant; wetting agent.

7 Applications in Pharmaceutical Formulation or Technology

Docusate sodium and docusate salts are widely used as anionic surfactants in pharmaceutical formulations. Docusate sodium is mainly used in capsule and direct-compression tablet formulations to assist in wetting and dissolution.(1) Docusate salts are also used in oral formulations as laxatives and fecal softeners; *see* Table I.

Table I: Uses of docusate sodium.

Use	Concentration (%)
IM injections	0.015
Surfactant (wetting/dispersing/emulsifying agent)	0.01–1.0
Tablet coating agent	20[a]
Tablet disintegrant	≈0.5

[a] Formulation of a tablet coating solution: 20% docusate sodium; 2–15% sodium benzoate; 0.5% propylene glycol; solution made in ethanol (70%).

8 Description

Docusate sodium is a white or almost white, waxlike, bitter tasting, plastic solid with a characteristic octanol-like odor. It is hygroscopic and usually available in the form of pellets, flakes, or rolls of tissue-thin material.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for docusate sodium.

Test	PhEur 2005	USP 28
Identification	+	+
Characters	+	—
Alkalinity	+	—
Bis(2-ethylhexyl) maleate	—	⩽0.4%
Chlorides	⩽350 ppm	—
Clarity of solution	—	+
Heavy metals	⩽10 ppm	⩽0.001%
Related nonionic substances	+	—
Residue on ignition	—	15.5–16.5%
Sodium sulfate	⩽2.0%	—
Water	⩽3.0%	⩽2.0%
Assay (dried basis)	98.0–100.5%	99.0–100.5%

10 Typical Properties

Acidity/alkalinity: pH = 5.8–6.9 (1% w/v aqueous solution).
Acid value: ⩽2.5
Critical micelle concentration: 0.11% w/v aqueous solution at 25°C.
Density: 1.16 g/cm^3
Hydroxyl value: 6.0–8.0
Interfacial tension: in water versus mineral oil at 25°C, *see* Table III.

Table III: Interfacial tension of docusate sodium.

Concentration (% w/v)	Interfacial tension (mN/m)
0.01	20.7
0.1	5.9
1.0	1.84

Iodine number: ⩽0.25
Melting point: 153–157°C
Moisture content: 1.51%
Saponification value: 240–253
Solubility: *see* Table IV.
Surface tension: *see* Table V.

Table IV: Solubility of docusate sodium.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	Soluble
Chloroform	1 in 1
Ethanol (95%)	1 in 3
Ether	1 in 1
Glycerin	Freely soluble
Vegetable oils	Soluble
Water	1 in 70 at 25°C[a]
	1 in 56 at 30°C
	1 in 44 at 40°C
	1 in 33 at 50°C
	1 in 25 at 60°C
	1 in 18 at 70°C

[a] In water, higher concentrations form a thick gel.

Table V: Surface tension of docusate sodium.

Concentration in water at 25°C (% w/v)	Surface tension (mN/m)
0.001	62.8
0.1	28.7
1.0	26.0

11 Stability and Storage Conditions

Docusate sodium is stable in the solid state when stored at room temperature. Dilute aqueous solutions of docusate sodium between pH 1–10 are stable at room temperature. However, at very low pH (<1) and very high pH (>10) docusate sodium solutions are subject to hydrolysis.

The solid material is hygroscopic and should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Electrolytes, e.g. 3% sodium chloride, added to aqueous solutions of docusate sodium can cause turbidity.(2,3) However, docusate sodium possesses greater tolerance to calcium, magnesium, and other polyvalent ions than do some other surfactants. Docusate sodium is incompatible with acids at pH <1 and with alkalis at pH >10.

13 Method of Manufacture

Maleic anhydride is treated with 2-ethylhexanol to produce dioctyl maleate, which is then reacted with sodium bisulfite.

14 Safety

Docusate salts are used in oral formulations as therapeutic agents for their fecal softening and laxative properties. As a laxative in adults, up to 500 mg of docusate sodium is administered daily in divided doses; in children over 6 months old, up to 75 mg in divided doses is used. The quantity of docusate sodium used as an excipient in oral formulations should therefore be controlled to avoid unintended laxative effects.(4) Adverse effects associated with docusate sodium include diarrhea, nausea, vomiting, abdominal cramps, and skin rashes. As with the chronic use of laxatives, the excessive use of docusate sodium may produce hypomagnesemia.(5)

Docusate salts are absorbed from the gastrointestinal tract and excreted in bile; they may cause alteration of the gastrointestinal epithelium.(6,7) The gastrointestinal or hepatic absorption of other drugs may also be affected by docusate salts, enhancing activity and possibly toxicity. Docusate sodium should not be administered with mineral oil as it may increase the absorption of the oil.

LD_{50} (mouse, IV): 0.06 g/kg(8)
LD_{50} (mouse, oral): 2.64 g/kg
LD_{50} (rat, IP): 0.59 g/kg
LD_{50} (rat, oral): 1.9 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Docusate sodium may be irritant to the eyes and skin, and when inhaled. Eye protection, gloves, and a dust mask or respirator are recommended. When heated to decomposition, docusate sodium emits toxic fumes.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (IM injections, oral capsules, suspensions, and tablets, also topical formulations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Docusate calcium; docusate potassium.

Docusate calcium

Empirical formula: $C_{40}H_{74}CaO_{14}S_2$
Molecular weight: 883.23
CAS number: [128-49-4]
Synonyms: 1,4-bis(2-ethylhexyl) sulfosuccinate, calcium salt; dioctyl calcium sulfosuccinate.
Appearance: white amorphous solid with a characteristic octanol-like odor.
Solubility: soluble 1 in less than 1 of ethanol (95%), chloroform, and ether, and 1 in 3300 of water; very soluble in corn oil and polyethylene glycol 400.

Docusate potassium

Empirical formula: $C_{20}H_{37}KO_7S$
Molecular weight: 460.67
CAS number: [7491-09-0]
Synonyms: dioctyl potassium sulfosuccinate; potassium 1,4-bis(2-ethylhexyl) sulfosuccinate.
Appearance: white amorphous solid with a characteristic octanol-like odor.
Solubility: soluble in ethanol (95%) and glycerin; sparingly soluble in water.

18 Comments

A convenient way of making a 1% w/v aqueous solution of docusate sodium is to add 1 g of solid to about 50 mL of water and to apply gentle heat. The docusate sodium dissolves in a short time and the resulting solution can be made up to 100 mL with water. Alternatively, 1 g may be soaked overnight in 50 mL of water and the additional water may then be added with gentle heating and stirring.

Docusate sodium may alter the dissolution characteristics of certain dosage forms and the bioavailability of some drugs.

The EINECS number for docusate sodium is 209-406-4.

19 Specific References

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7 Moriarty KJ, Kelly MJ, Beetham R, Clark ML. Studies on the mechanism of action of dioctyl sodium sulfosuccinate in the human jejunum. *Gut* 1985; **26**: 1008–1013.

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21 Authors

S Murdande.

22 Date of Revision

15 August 2005.

Edetic Acid

1 Nonproprietary Names

BP: Edetic acid
PhEur: Acidum edeticum
USPNF: Edetic acid

2 Synonyms

Dissolvine; edathamil; EDTA; ethylenediaminetetraacetic acid; (ethylenedinitrilo)tetraacetic acid; *Sequestrene AA*; tetracemic acid; *Versene Acid*.

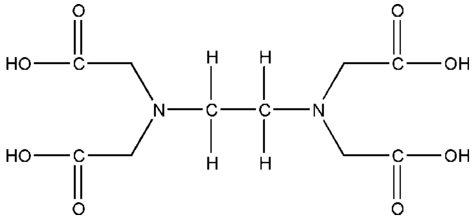
3 Chemical Name and CAS Registry Number

N,*N*-1,2-Ethanediylbis[*N*-(carboxymethyl)glycine] [60-00-4]

4 Empirical Formula and Molecular Weight

$C_{10}H_{16}N_2O_8$ 292.24

5 Structural Formula



6 Functional Category

Chelating agent.

7 Applications in Pharmaceutical Formulation or Technology

Edetic acid and edetate salts are used in pharmaceutical formulations, cosmetics, and foods as chelating agents. They form stable water-soluble complexes (chelates) with alkaline earth and heavy metal ions. The chelated form has few of the properties of the free ion, and for this reason chelating agents are often described as ‘removing’ ions from solution; this process is also called sequestering. The stability of the metal–edetate complex depends on the metal ion involved and also on the pH. The calcium chelate is relatively weak and will preferentially chelate heavy metals, such as iron, copper, and lead, with the release of calcium ions. For this reason, edetate calcium disodium is used therapeutically in cases of lead poisoning; *see also* Section 18.

Edetic acid and edetates are primarily used as antioxidant synergists, sequestering trace amounts of metal ions, particularly copper, iron, and manganese, that might otherwise catalyze autoxidation reactions. Edetic acid and edetates may be used alone or in combination with true antioxidants; the usual concentration employed being in the range 0.005–0.1% w/v. Edetates have been used to stabilize ascorbic acid; corticosteroids; epinephrine; folic acid; formaldehyde; gums and resins; hyaluronidase; hydrogen peroxide; oxytetracycline; penicillin; salicylic acid, and unsaturated fatty acids. Essential oils may be washed with a 2% w/v solution of edetate to remove trace metal impurities.

Edetic acid and edetates possess some antimicrobial activity but are most frequently used in combination with other antimicrobial preservatives owing to their synergistic effects. Many solutions used for the cleaning, storage, and wetting of contact lenses contain disodium edetate. Typically, edetic acid and edetates are used in concentrations of 0.01–0.1% w/v as antimicrobial preservative synergists; *see* Section 10.

Edetic acid and disodium edetate may also be used as water softeners since they will chelate the calcium and magnesium ions present in hard water; edetate calcium disodium is not effective. Many cosmetic and toiletry products, e.g., soaps, contain edetic acid as a water softener.

8 Description

Edetic acid occurs as a white crystalline powder.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for edetic acid.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Residue on ignition	—	⩽0.2%
Sulfated ash	⩽0.2%	—
Heavy metals	⩽20 ppm	⩽0.003%
Nitrilotriacetic acid	⩽0.1%	⩽0.3%
Iron	⩽80 ppm	⩽0.005%
Chloride	⩽200 ppm	—
Assay	98.0–101.0%	98.0–100.5%

10 Typical Properties

Acidity/alkalinity: pH = 2.2 for a 0.2% w/v aqueous solution.

Antimicrobial activity: edetic acid has some antimicrobial activity against Gram-negative microorganisms, *Pseudomonas aeruginosa*, some yeasts, and fungi; although this activity is insufficient for edetic acid to be used effectively as an antimicrobial preservative on its own.(1,2) However, when used with other antimicrobial preservatives, edetic acid demonstrates a marked synergistic effect in its antimicrobial activity. Edetic acid and edetates are therefore frequently used in combination with such preservatives as benzalkonium chloride; bronopol; cetrimide; imidurea; parabens; and phenols, especially chloroxylenol. Typically, edetic acid is used at a concentration of 0.1–0.15% w/v. In the presence of some divalent metal ions, such as Ca^{2+} or Mg^{2+}, the synergistic effect may be reduced or lost altogether. The addition of disodium edetate to phenylmercuric nitrate(3) and thimerosal(3,4) has also been reported to reduce the antimicrobial efficacy of the preservative. Edetic acid and iodine form a colorless addition compound that is bactericidal.

Dissociation constant:

$pK_{a1} = 2.00$;
$pK_{a2} = 2.67$;
$pK_{a3} = 6.16$;
$pK_{a4} = 10.26$.

Melting point: melts above 220°C, with decomposition.

Solubility: soluble in solutions of alkali hydroxides; soluble 1 in 500 of water.

11 Stability and Storage Conditions

Although edetic acid is fairly stable in the solid state, edetate salts are more stable than the free acid, which decarboxylates if heated above 150°C. Disodium edetate dihydrate loses water of crystallization when heated to 120°C. Edetate calcium disodium is slightly hygroscopic and should be protected from moisture.

Aqueous solutions of edetic acid or edetate salts may be sterilized by autoclaving, and should be stored in an alkali-free container.

Edetic acid and edetates should be stored in well-closed containers in a cool, dry place.

12 Incompatibilities

Edetic acid and edetates are incompatible with strong oxidizing agents, strong bases, and polyvalent metal ions such as copper, nickel, and copper alloy.

Edetic acid and disodium edetate behave as weak acids, displacing carbon dioxide from carbonates and reacting with metals to form hydrogen.

Other incompatibilities include the inactivation of certain types of insulin due to the chelation of zinc, and the chelation of trace metals in total parenteral nutrition (TPN) solutions following the addition of TPN additives stabilized with disodium edetate. Calcium disodium edetate has also been reported to be incompatible with amphotericin and with hydralazine hydrochloride in infusion fluids.

13 Method of Manufacture

Edetic acid may be prepared by the condensation of ethylenediamine with sodium monochloroacetate in the presence of sodium carbonate. An aqueous solution of the reactants is heated to about 90°C for 10 hours, then cooled, and hydrochloric acid is added to precipitate the edetic acid.

Edetic acid may also be prepared by the reaction of ethylenediamine with hydrogen cyanide and formaldehyde with subsequent hydrolysis of the tetranitrile, or under alkaline conditions with continuous extraction of ammonia.

See Section 17 for information on the preparation of edetate salts.

14 Safety

Edetic acid and edetates are widely used in topical, oral, and parenteral pharmaceutical formulations. They are also extensively used in cosmetics and food products.

Edetic acid is generally regarded as an essentially nontoxic and nonirritant material, although it has been associated with dose-related bronchoconstriction when used as a preservative in nebulizer solutions. It has therefore been recommended that nebulizer solutions for bronchodilation should not contain edetic acid.(5)

Edetates, particularly disodium edetate and edetate calcium disodium, are used in a greater number and variety of pharmaceutical formulations than the free acid.

Disodium edetate, trisodium edetate, and edetic acid readily chelate calcium and can, in large doses, cause calcium depletion (hypocalcemia) if used over an extended period or if administered too rapidly by intravenous infusion. If used in preparations for the mouth, they can also leach calcium from the teeth. In contrast, edetate calcium disodium does not chelate calcium.

Edetate calcium disodium is nephrotoxic and should be used with caution in patients with renal impairment.

The WHO has set an estimated acceptable daily intake for disodium edetate in foodstuffs at up to 2.5 mg/kg bodyweight.(6)

See also Section 18.

LD_{50} (mouse, IP): 0.25 g/kg(7)
LD_{50} (rat, IP): 0.397 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Edetic acid and edetates are mildly irritant to the skin, eyes, and mucous membranes. Ingestion, inhalation, and contact with the skin and eyes should therefore be avoided. Eye protection, gloves, and a dust mask are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (otic, rectal, and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

See also Section 17.

17 Related Substances

Dipotassium edetate; disodium edetate; edetate calcium disodium; sodium edetate; trisodium edetate.

Dipotassium edetate

Empirical formula: $C_{10}H_{14}K_2N_2O_8$

Molecular weight: 368.46

CAS number: [2001-94-7]

Synonyms: dipotassium edathamil; dipotassium ethylenediaminetetraacetate; edathamil dipotassium; edetate dipotassium; edetic acid dipotassium salt; EDTA dipotassium; *N*,*N*′-1,2-ethanediylbis[*N*-(carboxymethyl)glycine] dipotassium salt; ethylenebis(iminodiacetic acid) dipotassium salt; ethylenediaminetetraacetic acid dipotassium salt; (ethylenedinitrilo)tetraacetic acid dipotassium salt; tetracemate dipotassium.

Appearance: white crystalline powder.

Comments: The EINECS number for dipotassium edetate is 217-895-0.

Edetate calcium disodium

Empirical formula: $C_{10}H_{12}CaN_2Na_2O_8$

Molecular weight: 374.28

CAS number: [62-33-9] for the anhydrous material and [23411-34-9] for the dihydrate

Synonyms: calcium disodium edetate; calcium disodium ethylenediaminetetraacetate; calcium disodium (ethylenedinitrilo)tetraacetate; E385; edathamil calcium disodium; edetic acid calcium disodium salt; EDTA calcium; ethylenediaminetetraacetic acid calcium disodium chelate; [(ethylenedinitrilo)tetraacetato]calciate(2-) disodium; sodium calciumedetate; *Versene CA*.
Appearance: white or creamy-white colored, slightly hygroscopic, crystalline powder or granules; odorless, or with a slight odor; tasteless, or with a faint saline taste.
Acidity/alkalinity: pH = 4–5 for a 1% w/v aqueous solution.
Density (bulk): 0.69 g/cm^3
Solubility: practically insoluble in chloroform, ether, and other organic solvents; very slightly soluble in ethanol (95%); soluble 1 in 2 of water.
Method of manufacture: edetate calcium disodium may be prepared by the addition of calcium carbonate to a solution of disodium edetate.
Safety: *see also* Section 14.
LD$_{50}$ (mouse, IP): 4.5 g/kg$^{(7)}$
LD$_{50}$ (rabbit, IP): 6 g/kg
LD$_{50}$ (rabbit, oral): 7 g/kg
LD$_{50}$ (rat, IP): 3.85 g/kg
LD$_{50}$ (rat, IV): 3.0 g/kg
LD$_{50}$ (rat, oral): 10 g/kg
Regulatory status: GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (injections, oral capsules, solutions, suspensions, syrups, and tablets).
Comments: used in pharmaceutical formulations as a chelating agent in concentrations between 0.01–0.1% w/v. Usually edetate calcium disodium is used in pharmaceutical formulations in preference to disodium edetate or sodium edetate to prevent calcium depletion occurring in the body. In food products, edetate calcium disodium may also be used in flavors and as a color retention agent. Edetate calcium disodium occurs as the dihydrate, trihydrate, and anhydrous material.

Some pharmacopeias specify that edetate calcium disodium is the dihydrate, others that it is the anhydrous material. The USP 28 specifies that edetate calcium disodium is a mixture of the dihydrate and trihydrate but that the dihydrate predominates.

The EINECS number for edetate calcium disodium is 200-529-9.

Sodium edetate

Empirical formula: $C_{10}H_{12}N_2Na_4O_8$
Molecular weight: 380.20
CAS number: [64-02-8]
Synonyms: edetate sodium; edetic acid tetrasodium salt; EDTA tetrasodium; *N*,*N*′-1,2-ethanediylbis[*N*-(carboxymethyl)-glycine] tetrasodium salt; ethylenebis(iminodiacetic acid) tetrasodium salt; ethylenediaminetetraacetic acid tetrasodium salt; (ethylenedinitrilo)tetraacetic acid tetrasodium salt; *Sequestrene NA4*; tetracemate tetrasodium; tetracemin; tetrasodium edetate; tetrasodium ethylenebis(iminodiacetate); tetrasodium ethylenediaminetetraacetate; *Versene*.
Appearance: white crystalline powder.
Acidity/alkalinity: pH = 11.3 for a 1% w/v aqueous solution.
Melting point: >300°C
Solubility: soluble 1 in 1 of water.
Safety: *see also* Section 14.
LD$_{50}$ (mouse, IP): 0.33 g/kg$^{(7)}$
Regulatory status: included in the FDA Inactive Ingredients Guide (inhalations, injections, ophthalmic preparations, oral capsules and tablets, and topical preparations).
Comments: sodium edetate reacts with most divalent and trivalent metallic ions to form soluble metal chelates and is used in pharmaceutical formulations in concentrations between 0.01–0.1% w/v.

Trisodium edetate

Empirical formula: $C_{10}H_{13}N_2Na_3O_8$
Molecular weight: 358.20
CAS number: [150-38-9]
Synonyms: edetate trisodium; edetic acid trisodium salt; EDTA trisodium; *N*,*N*′-1,2-ethanediylbis[*N*-(carboxymethyl)glycine] trisodium salt; ethylenediaminetetraacetic acid trisodium salt; (ethylenedinitrilo)tetraacetic acid trisodium salt; *Sequestrene NA3*; trisodium ethylenediaminetetraacetate; *Versene-9*.
Appearance: white crystalline powder.
Acidity/alkalinity: pH = 9.3 for a 1% w/v aqueous solution.
Melting point: >300°C
Method of manufacture: trisodium edetate may be prepared by adding a solution of sodium hydroxide to disodium edetate.
Safety: *see also* Section 14.
LD$_{50}$ (mouse, IP): 0.3 g/kg$^{(7)}$
LD$_{50}$ (mouse, oral): 2.15 g/kg
LD$_{50}$ (rat, oral): 2.15 g/kg
Regulatory status: included in the FDA Inactive Ingredients Guide (topical preparations).
Comments: more soluble in water than either the disodium salt or the free acid. Trisodium edetate also occurs as the monohydrate and is used in pharmaceutical formulations as a chelating agent. The EINECS number for trisodium edetate is 205-758-8.

18 Comments

Other salts of edetic acid that are commercially available include diammonium, dimagnesium, ferric sodium, and magnesium disodium edetates. Therapeutically, a dose of 50 mg/kg body-weight of disodium edetate, as a slow infusion over a 24-hour period, with a maximum daily dose of 3 g, has been used as a treatment for hypercalcemia. For the treatment of lead poisoning, a dose of 60–80 mg/kg of edetate calcium disodium, as a slow infusion in two daily doses, for 5 days, has been used.

Chelation therapy using edetic acid has been widely used for the treatment of ischemic heart disease. However, it has been suggested that the therapeutic benefits of this treatment may be due to the changes in lifestyle of the patient rather than the administration of edetic acid (40 mg/kg by infusion over a 3-hour period).$^{(8)}$

The EINECS number for edetic acid is 200-449-4.

19 Specific References

1 Richards RME, Cavill RH. Electron microscope study of effect of benzalkonium chloride and edetate disodium on cell envelope of *Pseudomonas aeruginosa*. *J Pharm Sci* 1976; **65**: 76–80.
2 Whalley G. Preservative properties of EDTA. *Manuf Chem* 1991; **62**(9): 22–23.
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5 Beasley CRW, Rafferty P, Holgate ST. Bronchoconstrictor properties of preservatives in ipratropium bromide (Atrovent) nebuliser solution. *Br Med J* 1987; **294**: 1197–1198.

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7 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 1660.

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21 Authors

SC Owen.

22 Date of Revision

27 August 2005.

Erythorbic Acid

1 Nonproprietary Names

None adopted.

2 Synonyms

Araboascorbic acid; *d*-araboascorbic acid; D-2,3-didehydro-*erythro*-hexono-1,4-lactone; E315; erycorbin; *d*-erythorbic acid; D-*erythro*-hex-2-enoic acid; D-*erythro*-3-ketohexonic acid lactone; glucosaccharonic acid; D-isoascorbic acid; isovitamin C; γ-lactone; saccharosonic acid.

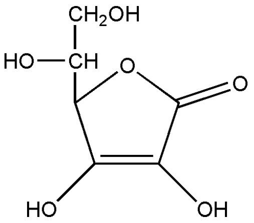
3 Chemical Name and CAS Registry Number

Isoascorbic acid [89-65-6]

4 Empirical Formula and Molecular Weight

$C_6H_8O_6$ 176.14

5 Structural Formula



6 Functional Category

Antioxidant.

7 Applications in Pharmaceutical Formulation or Technology

Erythorbic acid is a stereoisomer of L-ascorbic acid, and is used as an antioxidant in foods and oral pharmaceutical formulations. It has approximately 5% of the vitamin C activity of L-ascorbic acid.

8 Description

Erythorbic acid occurs as a white or slightly yellow-colored crystals or powder. It gradually darkens in color upon exposure to light.

9 Pharmacopeial Specifications

See Section 18.

10 Typical Properties

Acidity/alkalinity: pH = 2.1 (10% w/v aqueous solution at 25°C)
Density (bulk): 0.704 g/cm^3
Melting point: 164–171°C with decomposition at 184°C
Solubility: *see* Table I.
Specific rotation $[\alpha]_D^{20}$: −16.2 to −18.2° (10% w/v aqueous solution)

Table I: Solubility of erythorbic acid.

Solvent	Solubility at 25°C unless otherwise stated
Acetone	1 in 70
Ethanol (95%)	1 in 20
Ether	Practically insoluble
Methanol	1 in 5.5
Propylene glycol	1 in 6.7
Water	1 in 2.3
	1 in 1.8 at 38°C
	1 in 1.6 at 50°C

11 Stability and Storage Conditions

Erythorbic acid should be stored in an airtight container, protected from light, in a cool, dry place.

12 Incompatibilities

Erythorbic acid is incompatible with chemically active metals such as aluminum, copper, magnesium, and zinc. It is also incompatible with strong bases and strong oxidizing agents.

13 Method of Manufacture

Erythorbic acid is synthesized by the reaction between methyl 2-keto-D-gluconate and sodium methoxide. It can also be synthesized from sucrose, and produced from *Penicillium* spp.

14 Safety

Erythorbic acid is widely used in food applications as an antioxidant. It is also used in oral pharmaceutical applications as an antioxidant. Erythorbic acid is generally regarded as nontoxic and nonirritant when used as an excipient. Erythorbic acid is readily metabolized and does not affect the urinary excretion of ascorbic acid.

The WHO has set an acceptable daily intake of erythorbic acid and its sodium salt in foods at up to 5 mg/kg body-weight.(1)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. When heated to decomposition, erythorbic acid emits acrid smoke and irritating fumes.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral concentrate and tablets).

17 Related Substances

Ascorbic acid; sodium erythorbate

Sodium erythorbate

Empirical formula: $C_6H_7NaO_6$
Molecular weight: 198.11
CAS number: [7378-23-6]
Synonyms: E316; D-*erythro*-hex-2-enoic acid sodium salt; erythorbic acid sodium salt.
Acidity/alkalinity: pH = 7.2–7.9 for 10% w/v aqueous solution.
Melting point: 172°C
Solubility: soluble 1 in 6.5 of water. The sodium salt is less soluble in water than the free acid.
Comments: the EINECS number for sodium erythorbate is 228-973-6.

18 Comments

Although not currently included in any pharmacopeias, a specification for erythorbic acid is included in the Food Chemicals Codex and Japanese Pharmaceutical Excipients (JPE), *see* Table II.

The EINECS number for erythorbic acid is 201-928-0.

Table II: JPE 2004 specification for erythorbic acid.[2]

Test	JPE 2004
Identification	+
Clarity and color of solution	+
Melting point	166–172°C
Heavy metals	$\leqslant$20 ppm
Arsenic	$\leqslant$4 ppm
Loss on drying	$\leqslant$0.40%
Residue on ignition	$\leqslant$0.30%
Optical rotation at 20°C (10% w/v aqueous solution)	−16.2 to −18.2°
Assay	>99.0%

19 Specific References

1 FAO/WHO. Toxicological evaluation of certain food additives with a review of general principles and of specifications: seventeenth report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1974; No. **539**.
2 Japan Pharmaceutical Excipients Council. *Japanese Pharmaceutical Excipients 2004*. Tokyo: Yakuji Nippo, 2004: 281–282.

20 General References

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21 Authors

SC Owen, PJ Weller.

22 Date of Revision

25 May 2005.

Erythritol

1 Nonproprietary Names

PhEur: Erythritolum

2 Synonyms

(2*R*,3*S*)-Butane 1,2,3,4-tetrol; *C*Eridex*; E968; erythrite; erythroglucin; *meso*-erythritol; phycite; tetrahydroxybutane.

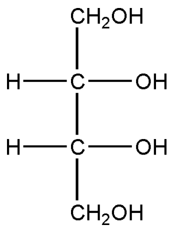
3 Chemical Name and CAS Registry Number

Erythritol [149-32-6]

4 Empirical Formula and Molecular Weight

$C_4H_{10}O_4$ 122.12

5 Structural Formula



6 Functional Category

Sweetening agent; tablet and capsule diluent; taste masking agent.

7 Applications in Pharmaceutical Formulation or Technology

Erythritol is a noncariogenic excipient used in a variety of pharmaceutical preparations, including in solid dosage forms as a tablet filler,(1) and in coatings.(2) It is also used in sugar-free lozenges,(3,4) and medicated chewing gum.(3)

Erythritol can also be used as a diluent in wet granulation in combination with moisture-sensitive drugs.(5) In buccal applications, such as medicated chewing gums, it is used because of its high negative heat of solution which provides a strong cooling effect.(3)

Erythritol is also used as a noncaloric sweetener in syrups;(6) it is used to provide sensorial profile-modifying properties with intense sweeteners; and it is also used to mask unwanted aftertastes.(7)

Erythritol is also used as a noncariogenic sweetener in toothpastes and mouthwash solutions.

See Table I.

Table I: Uses of erythritol.

Use	Concentration (%)
Tablet filler and binder	30.0–90.0%
Taste masking in solutions	0.5–3.0%
Oral care products	5.0–10.0%

8 Description

Erythritol is a sugar alcohol (polyol) that occurs as a white or almost white powder or granular or crystalline substance. It is pleasant tasting with a mild sweetness approximately 60–70% that of sucrose. It also has a high negative heat of solution that provides a strong cooling effect.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for erythritol.

Test	PhEur 2005
Identification (melting point)	119–122°C
Identification (IR)	+
Appearance of solution	+
Conductivity	+
Related substances	⩽2.0%
Lead	⩽0.5 ppm
Water	⩽0.5%
Microbial contamination	+
Bacterial endotoxins	+
Assay (anhydrous basis)	96.0–102.0%

10 Typical Properties

Acidity/alkalinity: pH = 5–7 at 25°C for a 5% w/v aqueous solution.

Boiling point: 329–331°C

Caloric value: 0.8 kJ/g

Density: 1.45 g/cm^3

Heat of solution: 22 kJ/mol

Hygroscopicity: erythritol is nonhygroscopic; it absorbs approximately 1% w/w of water at 95% relative humidity (RH).

Melting point: 121.5°C, with decomposition at 160°C.

Solubility: soluble 1 in 3 of water; slightly soluble in ethanol (95%); practically insoluble in ether and fats.

Viscosity (dynamic): 3 mPa s (3 cP) at 60°C for a 30% w/w solution.

11 Stability and Storage Conditions

Erythritol has very good thermal and chemical stability. It is nonhygroscopic, and at 25°C does not significantly absorb additional water up to a relative humidity (RH) of more than 80%. Erythritol resists decomposition both in acidic and alkaline media and remains stable for prolonged periods at pH 2–10.(8) When stored for up to 4 years in ambient conditions (20°C, 50% RH) erythritol has been shown to be stable.(5)

12 Incompatibilities

Erythritol is incompatible with strong oxidizing agents and strong bases.

13 Method of Manufacture

Erythritol is a starch-derived product. The starch is enzymatically hydrolyzed into glucose which is turned into erythritol via a fermentation process, using osmophilic yeasts or fungi (e.g. *Moniliella*, *Trigonopsis*, or *Torulopsis*).(9)

14 Safety

Erythritol is used in oral pharmaceutical formulations, confectionery, and food products. It is generally regarded as a nontoxic, nonallergenic, and nonirritant material.(10)

The low molecular weight of erythritol allows more than 90% of the ingested molecules to be rapidly absorbed from the small intestine;(11) it is not metabolized and is excreted unchanged in the urine. Erythritol has a low caloric value (0.8 kJ/g). The WHO has set an acceptable daily intake of 'not specified' for erythritol.(10)

Erythritol is noncariogenic; preliminary studies suggest that it may inhibit the formation of dental plaque.(12)

In general, erythritol is well-tolerated;(13) furthermore, excessive consumption does not cause laxative effects. There is no significant increase in the blood glucose level after oral intake, and glycemic response is very low, making erythritol suitable for diabetics.

LD_{50} (mouse, IP): 8–9 g/kg(10)
LD_{50} (rat, IV): 6.6 g/kg
LD_{50} (rat, oral): >13 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled. Eye protection and a dust mask or respirator are recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe.

17 Related Substances

Mannitol; sorbitol; xylitol.

18 Comments

Active ingredients can be granulated with erythritol and binders such as maltodextrin or carboxymethylcellulose, resulting in coarser granules with improved flowability.(3) Coprocessing erythritol with a small amount of maltodextrin results in a proprietary compound that is ideal for use in direct compression.(14)

A specification for erythritol is included in the Japanese Pharmaceutical Excipients (JPE).(15)

The EINECS number for erythritol is 205-737-3.

19 Specific References

1 Bi YX, Sunada Y, Yonezawa Y, Danjo K. Evaluation of rapidly disintegrating tablets prepared by a direct compression method. *Drug Dev Ind Pharm* 1999; **25**(5): 571–581.
2 Ohmori S, Ohno Y, Makino T, Kashihara T. Characteristics of erythritol and formulation of a novel coating with erythritol termed thin-layer sugarless coating. *Int J Pharm* 2004; **278**(2): 447–457.
3 Goossens J, Gonze M. Erythritol. *Manuf Confect* 2000; **80**(1): 71–75.
4 de Cock P. Chewing gum coating with a healthier crunch thanks to erythritol. *Confect Prod* 2003; **6**: 10–11.
5 Michaud J, Haest G. Erythritol: a new multipurpose excipient. *Pharmaceut Technol Eur* 2003; **15**(10): 69–72.
6 de Cock P. Erythritol: a novel noncaloric sweetener ingredient. In: Corti A, ed. *Low-Calorie Sweeteners: Present and Future*. Basel: Karger, 1999: 110–116.
7 de Cock P, Bechert CL. Erythritol. Functionality in noncaloric functional beverages. *Pure Appl Chem* 2002; **74**(7): 1281–1289.
8 Leutner C, ed. *Geigy Scientific Tables*, vol. **1**. Basel: Ciba Geigy, 1993: 84–85.
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13 Munro IC, Bernt WO, Borzella JF, *et al*. Erythritol: an interpretive summary of biochemical, metabolic, toxicologic and chemical data. *Food Chem Toxicol* 1998; **36**(12): 1139–1174.
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15 Japan Pharmaceutical Excipients Council. *Japanese Pharmaceutical Excipients 2004*. Tokyo: Yakuji Nippo, 2004: 283–284.

20 General References

Cerestar. Erythritol: the all-natural non-caloric bulk sweetener. http://www.eridex.com/english.html(accessed 24 May 2005).
Endo K, Amikawa S, Matsumoto A, *et al*. Erythritol-based dry powder of glucagons for pulmonary administration. *Int J Pharm* 2005; **290**: 63–71.
O'Brien Nabors L, Gelardi RC, eds. *Alternative Sweeteners*. New York: Marcel Dekker, 2001.

21 Authors

G Haest.

22 Date of Revision

24 May 2005.

Ethyl Acetate

1 Nonproprietary Names

BP: Ethyl acetate
PhEur: Ethylis acetas
USPNF: Ethyl acetate

2 Synonyms

Acetic acid ethyl ester; acetic ester; acetic ether; acetoxyethane; aethylis acetas; aethylium aceticum; ethyl ethanoate; vinegar naphtha.

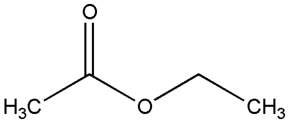
3 Chemical Name and CAS Registry Number

Ethyl acetate [141-78-6]

4 Empirical Formula and Molecular Weight

$C_4H_8O_2$ 88.1

5 Structural Formula



6 Functional Category

Flavoring agent; solvent.

7 Applications in Pharmaceutical Formulation or Technology

In pharmaceutical preparations, ethyl acetate is primarily used as a solvent, although it has also been used as a flavoring agent. As a solvent, it is included in topical solutions and gels, and in edible printing inks used for tablets.

Ethyl acetate has also been shown to increase the solubility of chlortalidone(1) and to modify the polymorphic crystal forms obtained for piroxicam pivalate(2) and mefenamic acid,(3) and has been used in the formulation of microspheres.(4,5) Its use as a chemical enhancer for the transdermal iontophoresis of insulin has been investigated.(6)

In food applications, ethyl acetate is mainly used as a flavoring agent. It is also used in artificial fruit essence and as an extraction solvent in food processing.

8 Description

Ethyl acetate is a clear, colorless, volatile liquid with a pleasant fruity, fragrant, and slightly acetous odor, and has a pleasant taste when diluted. Ethyl acetate is flammable.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for ethyl acetate.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Boiling point	76–78°C	—
Appearance of solution	+	—
Acidity	+	+
Specific gravity	0.898–0.902	0.894–0.898
Refractive index	1.370–1.373	—
Readily carbonizable substances	+	+
Reaction with sulfuric acid	+	—
Chromatographic purity	+(a)	+
Residue on evaporation	⩽30 ppm	⩽0.02%
Water	⩽0.1%	—
Limit of methyl compounds	—	+
Organic volatile impurities	—	+
Related substances	+	—
Assay	—	99.0–100.5%

(a) The PhEur 2005 lists impurities in ethyl acetate as methyl acetate, ethanol, and methanol.

10 Typical Properties

Autoignition temperature: 486.1°C
Boiling point: 77°C
Dielectric constant: 6.11
Density: 0.902 g/cm^3 at 20°C
Explosive limit: 2.2–11.5% (volume in air)
Flash point:
+7.2°C (open cup);
−5.0°C (closed cup).
Freezing point: −83.6°C
Partition coefficient: Log *P* (octanol/water) = 0.7
Refractive index: n_D^{20} = 1.3719
Solubility: soluble 1 in 10 of water at 25°C; ethyl acetate is more soluble in water at lower temperatures than at higher temperatures. Miscible with acetone, chloroform, dichloromethane, ethanol (95%), and ether, and with most other organic liquids.
Vapor density: 3.04 (air = 1)

11 Stability and Storage Conditions

Ethyl acetate should be stored in an airtight container, protected from light and at a temperature not exceeding 30°C. Ethyl acetate is slowly decomposed by moisture and becomes acidic; the material can absorb up to 3.3% w/w water.

Ethyl acetate decomposes on heating to produce ethanol and acetic acid, and will emit acrid smoke and irritating fumes. It is flammable and its vapor may travel a considerable distance to an ignition source and cause a 'flashback'.

The alkaline hydrolysis of ethyl acetate has been shown to be inhibited by polyethylene glycol and by mixed micelle systems.(7)

12 Incompatibilities

Ethyl acetate can react vigorously with strong oxidizers, strong alkalis, strong acids, and nitrates to cause fires or explosions. It also reacts vigorously with chlorosulfonic acid, lithium aluminum hydride, 2-chloromethylfuran, and potassium *tert*-butoxide.

13 Method of Manufacture

Ethyl acetate can be manufactured by the slow distillation of a mixture of ethanol and acetic acid in the presence of concentrated sulfuric acid. It has also been prepared from ethylene using an aluminum alkoxide catalyst.

14 Safety

Ethyl acetate is used in foods and oral and topical pharmaceutical formulations. It is generally regarded as a relatively nontoxic and nonirritant material when used as an excipient.

However, ethyl acetate may be irritant to mucous membranes and high concentrations may cause central nervous system depression. Potential symptoms of overexposure include irritation of the eyes, nose, and throat, narcosis, and dermatitis.

Ethyl acetate has not been shown to be a human carcinogen or a reproductive or developmental toxin.

The WHO has set an estimated acceptable daily intake of ethyl acetate at up to 25 mg/kg body-weight.(8)

In the UK, it has been recommended that ethyl acetate be temporarily permitted for use as a solvent in food and that the maximum concentration consumed in food should be set at 1000 ppm.(9)

LD_{50} (cat, SC): 3.00 g/kg(10)
LD_{50} (guinea-pig, oral): 5.50 g/kg
LD_{50} (guinea-pig, SC): 3.00 g/kg
LD_{50} (mouse, IP): 0.709 g/kg
LD_{50} (mouse, oral): 4.10 g/kg
LD_{50} (rabbit, oral): 4.935 g/kg
LD_{50} (rat, oral): 5.62 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. In the UK, the occupational exposure limit for ethyl acetate is 400 ppm (short-term) and 200 ppm (long-term).(11)

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral tablets and sustained-action tablets; topical and transdermal preparations). Included in nonparenteral medicines licensed in the UK (tablets, topical solutions, and gels). Ethyl acetate is also accepted for use in food applications in a number of countries including the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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18 Comments

The following azeotropic mixtures have been reported:

Ethyl acetate (93.9% w/w)–water (6.1% w/w), boiling point 70.4°C
Ethyl acetate (83.2% w/w)–water (7.8% w/w)–ethanol (9.0% w/w), boiling point 70.3°C
Ethyl acetate (69.4%)–ethanol (30.6%), boiling point 71.8°C
Ethyl acetate (77%)–propan-2-ol (23%), boiling point 74.8°C

A specification for ethyl acetate is contained in the Food Chemicals Codex (FCC).

The EINECS number for ethyl acetate is 205-500-4.

19 Specific References

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3 Romero S, Escalera B, Bustamante P. Solubility behavior of polymorphs I and II of mefenamic acid in solvent mixtures. *Int J Pharm* 1999; **178**: 193–202.
4 Abu-Izza K, Garcia-Contreras L, Lu DR. Preparation and evaluation of zidovudine-loaded sustained-release microspheres. 2. Optimization of multiple response variables. *J Pharm Sci* 1996; **85**(6): 572–576.
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6 Pillai O, Nair V, Panchagnula R. Transdermal iontophoresis of insulin: IV. Influence of chemical enhancers. *Int J Pharm* 2004; **269**(1): 109–120.
7 Xiancheng Z, Xiaonan C, Ziming Q, Qian W. The alkaline hydrolysis of ethyl acetate and ethyl propionate in single and mixed micellar solutions. *J Disper Sci Technol* 1996; **17**(3): 339–348.
8 FAO/WHO. Specifications for the identity and purity of food additives and their toxicological evaluation: some flavouring substances and non-nutritive sweetening agents. Eleventh report of the Joint FAO/WHO Expert Committee on Food Additives. *World Health Organ Tech Rep Ser* 1968; No. 383.
9 Ministry of Agriculture, Fisheries and Food. *Report on the Review of Solvents in Food, FAC/REP/25*. London: HMSO, 1978.
10 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials,* 11th edn. New York: Wiley, 2004: 1625.
11 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.

20 General References

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21 Authors

CG Cable.

22 Date of Revision

19 August 2005.

Ethyl Lactate

1 Nonproprietary Names

None adopted.

2 Synonyms

Actylol; *Acytol*; ethyl α-hydroxypropionate; ethyl-2-hydroxypropanoate; ethyl-2-hydroxypropionate; ethyl-*S*-(–)-2-hydroxypropionate; 2-hydroxypropanoic acid ethyl ester; lactic acid ethyl ester; propanoic acid 2-hydroxy-ethyl ester; *Purasolv EL*; *Solactol*.

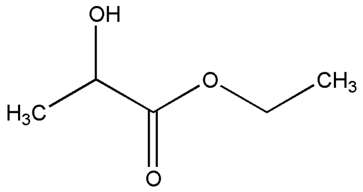
3 Chemical Name and CAS Registry Number

2-Hydroxy-propanoic acid ethyl ester [97-64-3]

4 Empirical Formula and Molecular Weight

$C_5H_{10}O_3$ 118.13

5 Structural Formula



6 Functional Category

Film-former; flavoring agent; solvent or co-solvent in liquid formulations.

7 Applications in Pharmaceutical Formulation or Technology

Ethyl lactate is used as a solvent or co-solvent in liquid formulations(1,2) and recently as a co-solvent in emulsions and microemulsion technologies. It has also been used as a solvent for nitrocellulose, cellulose acetate, cellulose ethers, polyvinyl and other resins.(3) It has been applied topically in the treatment of acne vulgaris,(4,5) where it accumulates in the sebaceous glands and is hydrolyzed to ethanol and lactic acid, lowering the skin pH and exerting a bactericidal effect.

8 Description

Ethyl lactate occurs as a clear colorless liquid with a sharp characteristic odor.

9 Pharmacopeial Specifications

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10 Typical Properties

Acidity/alkalinity: pH = 7 (10% w/v aqueous solution)
Boiling point: 154–155°C
Density: 1.0328 at 20°C
Explosion limits: 1.5–11.4%
Flash point: 46°C
Heat of combustion: 6.5 kcal/g
Melting point: –26.0°C
Refractive index: n_D^{20} = 1.412–1.414
Solubility: miscible with water (with partial decomposition), ethanol (95%), ether, chloroform, ketones, esters, and hydrocarbons.
Viscosity (dynamic): 0.0261 mPa s at 20°C
Vapor density: 4.07 (air = 1)
Vapor pressure: 0.732 kPa at 30°C

11 Stability and Storage Conditions

Stable at normal temperature and pressure. Ethyl lactate is a flammable liquid and vapor. Store in a cool, dry, and well-ventilated location away from any fire hazard area, in a tightly closed container.

12 Incompatibilities

Incompatible with bases or strong alkalis and may cause fire or explosion with strong oxidizing agents.

13 Method of Manufacture

Ethyl lactate is produced by the esterification of lactic acid with ethanol in the presence of a little mineral oil, or by combination of acetaldehyde with hydrocyanic acid to form acetaldehyde cyanhydrin. This is followed by treatment with ethanol (95%) and hydrochloric or sulfuric acid. Purification is achieved using fractional distillation. The commercial product is a racemic mixture.

14 Safety

Ethyl lactate is used as a flavoring agent in pharmaceutical preparations, and is found in food products. The estimated acceptable daily intake for lactic acid is 12.5 mg/kg bodyweight.

In general, lactate esters have an oral $LD_{50} > 2000$ mg/kg; and the inhalation LC_{50} is generally above 5000 mg/m^3. They have the potential of causing eye and skin irritation (on prolonged contact), but not sensitization.(6) Ethyl lactate is moderately toxic by intraperitoneal, subcutaneous, and intravenous routes. There is low oral and skin contact toxicity; although ingestion may cause nausea, stomach and throat pain, and narcosis. Inhalation of concentrated vapor of ethyl lactate may cause irritation of the mucous membranes, drowsiness, and narcosis.

LD_{50} (rat, oral): >5.0 g/kg(7)
LD_{50} (mouse, oral): 2.5 g/kg
LD_{50} (mouse, SC): 2.5 g/kg
LD_{50} (mouse, IV): 0.6 g/kg
LD_{50} (rabbit, skin): >5.0 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Avoid skin and eye contact; eye goggles should be worn, or a full face shield where splashing may occur.

There is a slight explosion hazard in the form of vapor when it is exposed to flame. Avoid ignition sources and use adequate ventilation to keep vapor and mist as low as possible.

When heated to decomposition, it emits acrid smoke and irritating fumes. Facial respirators are recommended when dealing with excessive amounts or with prolonged exposure to the compound.

16 Regulatory Status

GRAS listed. Reported in the EPA TSCA Inventory.

17 Related Substances

n-Butyl lactate; methyl lactate.

n-Butyl lactate

Empirical formula: $C_7H_{14}O_3$
Molecular weight: 146.2
CAS number: [138-22-7]
Synonyms: butyl α-hydroxypropionate; propanoic acid 2-hydroxy butyl ester; lactic acid butyl ester; *Purasolv BL*.
Boiling point: 188°C
Melting point: –43°C
Solubility: partially miscible with water and most organic solvents.
Comments: *n*-butyl lactate is used as a flavoring agent in pharmaceutical preparations.

The EINECS number for *n*-butyl lactate is 205-316-4.

Methyl lactate

Empirical formula: $C_4H_8O_3$
Molecular weight: 104
CAS number: [547-64-8]
Synonyms: methyl hydroxy propionate; *Purasolv ML*.
Appearance: methyl lactate occurs as a clear, colorless liquid.
Boiling point: 143.9°C
Comments: methyl lactate is used as a cellulose acetate solvent.

18 Comments

Ethyl lactate is found in food products as a flavoring agent; owing to its biodegradability, ethyl lactate is replacing many solvents in many household products, including packaging, plastics, paints, paint strippers, grease removers, cleansers, aerosols, adhesives, and varnishes.

Ethyl lactate is specified as a flavor chemical in the Food Chemicals Codex (FCC).(8)

The EINECS number for ethyl lactate is 202-598-0.

19 Specific References

1 Christensen JM, Suvanakoot U, Ayres JW, Tavipatana W. Ethyl lactate–ethanol–water cosolvent for intravenous theophylline. *Res Commun Chem Pathol Pharmacol* 1985; **50**(1): 147–150.
2 Mottu F, Laurent A, Rufenacht DA, Doelker E. Organic solvents for pharmaceutical parenterals and embolic liquids: A review of toxicity data. *PDA J Pharm Sci Tech* 2000; **54**(6): 456–469.
3 Siew LF, Basit AW, Newton JM. The properties of amylose–ethylcellulose films cast from organic-based solvents as potential coatings for colonic drug delivery. *Eur J Pharm Sci* 2000; **11**(2): 133–139.
4 George D, Prottery C, Black JG, *et al*. Ethyl lactate as a treatment for acne. *Br J Dermatol* 1983; **108**(2): 228–233.
5 Prottey C, George D, Leech RW, *et al*. The mode of action of ethyl lactate as a treatment for acne. *Br J Dermatol* 1984; **110**(4): 475–485.
6 Clary JJ, Feron VJ, van Velthuijsen JA. Safety assessment of lactate esters. *Regul Toxicol Pharmacol* 1998; **27**(2): 88–97.
7 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 2197.
8 *Food Chemicals Codex*, 4th edn. Washington, DC: National Academy Press, 1996: 490–491.

20 General References

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21 Authors

O AbuBaker.

22 Date of Revision

15 August 2005.

Ethyl Maltol

1 Nonproprietary Names

None adopted.

2 Synonyms

2-Ethyl pyromeconic acid; 3-hydroxy-2-ethyl-4-pyrone; *Veltol Plus*.

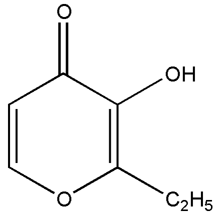
3 Chemical Name and CAS Registry Number

2-Ethyl-3-hydroxy-4*H*-pyran-4-one [4940-11-8]

4 Empirical Formula and Molecular Weight

$C_7H_8O_3$ 140.14

5 Structural Formula



6 Functional Category

Flavor enhancer; flavoring agent.

7 Applications in Pharmaceutical Formulation or Technology

Ethyl maltol is used in pharmaceutical formulations and food products as a flavoring agent or flavor enhancer in applications similar to maltol. It has a flavor and odor 4–6 times as intense as maltol. Ethyl maltol is used in oral syrups at concentrations of about 0.004% w/v and also at low levels in perfumery.

8 Description

White crystalline solid with characteristic, very sweet, caramel-like odor and taste. In dilute solution it possesses a sweet, fruitlike flavor and odor.

9 Pharmacopeial Specifications

See Section 19.

10 Typical Properties

Melting point: 89–93°C
Solubility: *see* Table I.

Table I: Solubility of ethyl maltol.

Solvent	Solubility at 20°C
Chloroform	1 in 5
Ethanol (95%)	1 in 10
Glycerin	1 in 500
Propan-2-ol	1 in 11
Propylene glycol	1 in 17
Water	1 in 55

11 Stability and Storage Conditions

Solutions may be stored in glass or plastic containers. The bulk material should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

—

13 Method of Manufacture

Unlike maltol, ethyl maltol does not occur naturally. It may be prepared by treating α-ethylfurfuryl alcohol with a halogen to produce 4-halo-6-hydroxy-2-ethyl-2*H*-pyran-3(6*H*)-one, which is converted to ethyl maltol by hydrolysis.

14 Safety

In animal feeding studies, ethyl maltol has been shown to be well tolerated with no adverse toxic, reproductive, or embryogenic effects. It has been reported that while the acute toxicity of ethyl maltol, in animal studies, is slightly greater than maltol; with repeated dosing the opposite is true.(1) Although an acceptable daily intake for ethyl maltol has not been set the WHO has set an acceptable daily intake for maltol at up to 1 mg/kg body-weight.(2)

LD_{50} (chicken, oral): 1.27 g/kg(3)
LD_{50} (rat, oral): 1.15 g/kg
LD_{50} (mouse, oral): 0.78 g/kg
LD_{50} (mouse, SC): 0.91 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Ethyl maltol should be used in a well-ventilated environment. Dust may be irritant and eye protection and gloves are recommended.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral syrup).

17 Related Substances

Maltol.

18 Comments

See Maltol for further information.

Although not included in any pharmacopeias, a specification for ethyl maltol is contained in the Food Chemicals Codex (FCC), *see* Table II.(4)

Table II: Food Chemicals Codex specifications for ethyl maltol.

Test	FCC 1996
Identification	+
Heavy metals (as lead)	⩽0.002%
Lead	⩽10 ppm
Residue on ignition	⩽0.2%
Water	⩽0.5%
Assay (dried basis)	⩾99.0%

19 Specific References

1 Gralla EJ, Stebbins RB, Coleman GL, Delahunt CS. Toxicity studies with ethyl maltol. *Toxicol Appl Pharmacol* 1969; **15**: 604–613.

2 FAO/WHO. Evaluation of certain food additives. Twenty-fifth report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1981; No. 669.

3 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 1692.

4 *Food Chemicals Codex*, 4th edn. Washington, DC: National Academy Press, 1996: 138.

20 General References

Allen LV. Featured excipient: flavor enhancing agents. *Int J Pharm Compound* 2003; 7(1): 48–50.

21 Authors

PJ Weller.

22 Date of Revision

14 August 2005.

Ethyl Oleate

1 Nonproprietary Names

BP: Ethyl oleate
PhEur: Ethylis oleas
USPNF: Ethyl oleate

2 Synonyms

Ethyl 9-octadecenoate; *Kessco EO*; oleic acid, ethyl ester.

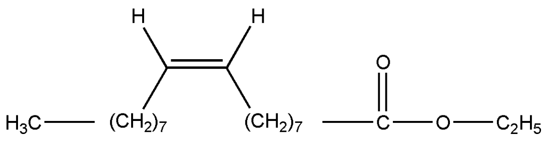
3 Chemical Name and CAS Registry Number

(*Z*)-9-Octadecenoic acid, ethyl ester [111-62-6]

4 Empirical Formula and Molecular Weight

$C_{20}H_{38}O_2$ 310.51

5 Structural Formula



6 Functional Category

Oleaginous vehicle; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Ethyl oleate is primarily used as a vehicle in certain parenteral preparations intended for intramuscular administration. It has also been used as a solvent for drugs formulated as biodegradable capsules for subdermal implantation(1) and in the preparation of microemulsions containing cyclosporin.(2)

Ethyl oleate is a suitable solvent for steroids and other lipophilic drugs. Its properties are similar to those of almond oil and peanut oil. However, it has the advantage that it is less viscous than fixed oils and is more rapidly absorbed by body tissues.(3)

Ethyl oleate has also been evaluated as a vehicle for subcutaneous injection.(4)

8 Description

Ethyl oleate occurs as a pale yellow to almost colorless, mobile, oily liquid with a taste resembling that of olive oil and a slight, but not rancid odor.

Ethyl oleate is described in the USPNF 23 as consisting of esters of ethyl alcohol and high molecular weight fatty acids, principally oleic acid. A suitable antioxidant may be included.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for ethyl oleate.

Test	PhEur 2005	USPNF 23
Characters	+	—
Identification	+	+
Specific gravity	0.866–0.874	0.866–0.874
Viscosity	—	⩾5.15 mPa s
Refractive index	—	1.443–1.450
Acid value	⩽0.5	⩽0.5
Iodine value	75–90	75–85
Saponification value	177–188	177–188
Peroxide value	⩽10	—
Oleic acid	⩾ 60.0%	—
Water content	⩽1.0%	—
Total ash	⩽0.1%	—

10 Typical Properties

Boiling point: 205–208°C (some decomposition)
Flash point: 175.3°C
Freezing point: ≈−32°C
Moisture content: at 20°C and 52% relative humidity, the equilibrium moisture content of ethyl oleate is 0.08%.
Solubility: miscible with chloroform, ethanol (95%), ether, fixed oils, liquid paraffin, and most other organic solvents; practically insoluble in water.
Surface tension: 32.3 mN/m (32.3 dynes/cm) at 25°C(3)
Viscosity (dynamic): 3.9 mPa s (3.9 cP) at 25°C(3)
Viscosity (kinematic): 0.046 mm^2/s (4.6 cSt) at 25°C(3)

11 Stability and Storage Conditions

Ethyl oleate should be stored in a cool, dry place in a small, well-filled, well-closed container, protected from light. When a partially filled container is used, the air should be replaced by nitrogen or another inert gas. Ethyl oleate oxidizes on exposure to air, resulting in an increase in the peroxide value. It remains clear at 5°C, but darkens in color on standing. Antioxidants are frequently used to extend the shelf life of ethyl oleate. Protection from oxidation for over 2 years has been achieved by storage in amber glass bottles with the addition of combinations of propyl gallate, butylated hydroxyanisole, butylated hydroxytoluene, and citric or ascorbic acid.(5,6) A concentration of 0.03% w/v of a mixture of propyl gallate (37.5%), butylated hydroxytoluene (37.5%), and butylated hydroxyanisole (25%) was found to be the best antioxidant for ethyl oleate.(6)

Ethyl oleate may be sterilized by heating at 150°C for 1 hour.

12 Incompatibilities

Ethyl oleate dissolves certain types of rubber and causes others to swell.(7,8) It may also react with oxidizing agents.

13 Method of Manufacture

Ethyl oleate is prepared by the reaction of ethanol with oleoyl chloride in the presence of a suitable hydrogen chloride acceptor.

14 Safety

Ethyl oleate is generally considered to be of low toxicity but ingestion should be avoided. Ethyl oleate has been found to cause minimal tissue irritation.(9) No reports of intramuscular irritation during use have been recorded.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and nitrile gloves are recommended. Ethyl oleate is flammable.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (transdermal preparation). Included in parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Methyl oleate; oleic acid.

Methyl oleate

Empirical formula: $C_{19}H_{36}O_2$
Molecular weight: 296.49
CAS number: [112-69-9]
Synonyms: methyl 9-octadecenoate; (*Z*)-9-octadecenoic acid, methyl ester.
Boiling point: 168–170°C
Density: 0.879 g/cm^3
Iodine number: 85.6
Refractive index: $n_D^{26} = 1.4510$
Solubility: miscible with ethanol (95%) and ether.
Comments: prepared by refluxing oleic acid with *p*-toluenesulfonic acid in methanol.

18 Comments

The EINECS number for ethyl oleate is 203-889-5.

19 Specific References

1 Ory SJ, Hammond CB, Yancy SG, *et al.* Effect of a biodegradable contraceptive capsule (Capronor) containing levonorgestrel on gonadotropin, estrogen and progesterone levels. *Am J Obstet Gynecol* 1983; **145**: 600–605.
2 Kim C-K, Ryuu S-A, Park K-M. Preparation and physicochemical characterisation of phase inverted water/oil microemulsion containing cyclosporin A. *Int J Pharm* 1997; **147**: 131–134.
3 Howard JR, Hadgraft J. The clearance of oily vehicles following intramuscular and subcutaneous injections in rabbits. *Int J Pharm* 1983; **16**: 31–39.
4 Radwan M. *In vivo* screening model for excipients and vehicles used in subcutaneous injections. *Drug Dev Ind Pharm* 1994; **20**: 2753–2762.
5 Alemany P, Del Pozo A. Autoxidation of ethyl oleate: protection with antioxidants [in Spanish]. *Galenica Acta* 1963; **16**: 335–338.
6 Nikolaeva NM, Gluzman MK. Conditions for stabilizing ethyl oleate during storage [in Russian]. *Farmatsiya* 1977; **26**: 25–28.
7 Dexter MB, Shott MJ. The evaluation of the force to expel oily injection vehicles from syringes. *J Pharm Pharmacol* 1979; **31**: 497–500.
8 Halsall KG. Calciferol injection and plastic syringes [letter]. *Pharm J* 1985; **235**: 99.
9 Hem SL, Bright DR, Banker GS, Pogue JP. Tissue irritation evaluation of potential parenteral vehicles. *Drug Dev Commun* 1974–75; **1**(5): 471–477.

20 General References

Spiegel AJ, Noseworthy MM. Use of nonaqueous solvents in parenteral products. *J Pharm Sci* 1963; **52**: 917–927.

21 Authors

CG Cable.

22 Date of Revision

21 August 2005.

Ethyl Vanillin

1 Nonproprietary Names

USPNF: Ethyl vanillin

2 Synonyms

Bourbonal; ethylprotal; ethylprotocatechuic aldehyde; 4-hydroxy-3-ethoxybenzaldehyde; *Rhodiarome*; vanillal.

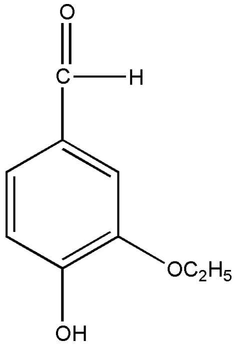
3 Chemical Name and CAS Registry Number

3-Ethoxy-4-hydroxybenzaldehyde [121-32-4]

4 Empirical Formula and Molecular Weight

$C_9H_{10}O_3$ 166.18

5 Structural Formula



6 Functional Category

Flavoring agent.

7 Applications in Pharmaceutical Formulation or Technology

Ethyl vanillin is used as an alternative to vanillin, i.e., as a flavoring agent in foods, beverages, confectionery, and pharmaceuticals. It is also used in perfumery.

Ethyl vanillin possesses a flavor and odor approximately three times as intense as vanillin, hence the quantity of material necessary to produce an equivalent vanilla flavor may be reduced, causing less discoloration to a formulation and potential savings in material costs. However, exceeding certain concentration limits may impart an unpleasant, slightly bitter taste to a product due to the intensity of the ethyl vanillin flavor. *See* Table I.

Table I: Uses of ethyl vanillin.

Use	Concentration (%)
Foods and confectionery	0.002–0.025
Oral syrups	0.01

8 Description

White or slightly yellowish crystals with a characteristic intense vanilla odor and flavor.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for ethyl vanillin.

Test	USPNF 23
Identification	+
Melting range	76.0–78.0°C
Loss on drying	≤1.0%
Residue on ignition	≤0.1%
Organic volatile impurities	+
Assay (dried basis)	98.0–101.0%

10 Typical Properties

Boiling point: 285°C
Density (bulk): 1.05 g/cm^3
Flash point: 127°C
Melting point: 76–78°C
Solubility: *see* Table III.

Table III: Solubility of ethyl vanillin.

Solvent	Solubility at 20°C unless otherwise stated
Alkaline hydroxide solutions	Freely soluble
Chloroform	Freely soluble
Ethanol (95%)	1 in 2
Ether	Freely soluble
Glycerin	Soluble
Propylene glycol	Soluble
Water	1 in 250
	1 in 100 at 50°C

11 Stability and Storage Conditions

Store in a well-closed container, protected from light, in a cool, dry place. *See* Vanillin for further information.

12 Incompatibilities

Ethyl vanillin is unstable in contact with iron or steel forming a red-colored, flavorless compound. In aqueous media with neomycin sulfate or succinylsulfathiazole, tablets of ethyl vanillin produced a yellow color.(1) *See* Vanillin for other potential incompatibilities.

13 Method of Manufacture

Unlike vanillin, ethyl vanillin does not occur naturally. It may be prepared synthetically by the same methods as vanillin, using guethol instead of guaiacol as a starting material; *see* Vanillin.

14 Safety

Ethyl vanillin is generally regarded as an essentially nontoxic and nonirritant material. However, cross-sensitization with other structurally similar molecules may occur; *see* Vanillin.

The WHO has allocated an acceptable daily intake for ethyl vanillin of up to 3 mg/kg body-weight.(2)

LD_{50} (guinea pig, IP): 1.14 g/kg(3,4)
LD_{50} (mouse, IP): 0.75 g/kg
LD_{50} (rabbit, oral): 3 g/kg
LD_{50} (rabbit, SC): 2.5 g/kg
LD_{50} (rat, oral): 1.59 g/kg
LD_{50} (rat, SC): 3.5–4.0 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended. Heavy airborne concentrations of dust may present an explosion hazard.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral capsules, suspensions, and syrups). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Vanillin.

18 Comments

Ethyl vanillin can be distinguished analytically from vanillin by the yellow color developed in the presence of concentrated sulfuric acid. The EINECS number for ethyl vanillin is 204-464-7.

19 Specific References

1 Onur E, Yalcindag ON. Double incompatibility of ethyl vanillin (vanillal) in compressed tablets [in French]. *Bull Soc Pharm Bordeaux* 1970; **109**(2): 49–51.
2 FAO/WHO. Evaluation of certain food additives and contaminants. Forty-fourth report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1995; No. 859.
3 Sweet DV, ed. *Registry of Toxic Effects of Chemical Substances*. Cincinnati: US Department of Health, 1987: 721.
4 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 1729.

20 General References

Rees DI. Determination of vanillin and ethyl vanillin in food products. *Chem Ind* 1965; **1**: 16–17.

21 Authors

PJ Weller.

22 Date of Revision

14 August 2005.

Ethylcellulose

1 Nonproprietary Names

BP: Ethylcellulose
PhEur: Ethylcellulosum
USPNF: Ethylcellulose

2 Synonyms

Aquacoat ECD; *Aqualon*; E462; *Ethocel*; *Surelease*.

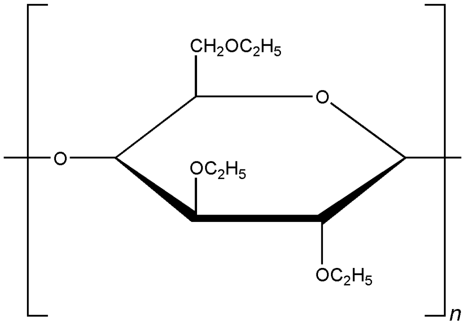
3 Chemical Name and CAS Registry Number

Cellulose ethyl ether [9004-57-3]

4 Empirical Formula and Molecular Weight

Ethylcellulose with complete ethoxyl substitution (DS = 3) is $C_{12}H_{23}O_6(C_{12}H_{22}O_5)_nC_{12}H_{23}O_5$ where n can vary to provide a wide variety of molecular weights. Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of β-anhydroglucose units joined together by acetal linkages.

5 Structural Formula



6 Functional Category

Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Ethylcellulose is widely used in oral and topical pharmaceutical formulations; *see* Table I.

The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules.(1–8) Ethylcellulose coatings are used to modify the release of a drug,(7–10) to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethylcellulose to inhibit oxidation. Modified-release tablet formulations may also be produced using ethylcellulose as a matrix former.(11–14)

Ethylcellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films. Higher-viscosity ethylcellulose grades tend to produce stronger and more durable films. Ethylcellulose films may be modified to alter their solubility,(15) by the addition of hypromellose(16) or a plasticizer;(17–19) *see* Section 18. An aqueous polymer dispersion (or latex) of ethylcellulose such as *Aquacoat ECD* (FMC Biopolymer) or *Surelease* (Colorcon) may also be used to produce ethylcellulose films without the need for organic solvents.

Drug release through ethylcellulose-coated dosage forms can be controlled by diffusion through the film coating. This can be a slow process unless a large surface area (e.g. pellets or granules compared with tablets) is utilized. In those instances, aqueous ethylcellulose dispersions are generally used to coat granules or pellets. Ethylcellulose-coated beads and granules have also demonstrated the ability to absorb pressure and hence protect the coating from fracture during compression.(19)

High-viscosity grades of ethylcellulose are used in drug microencapsulation.(10,20–22)

Release of a drug from an ethylcellulose microcapsule is a function of the microcapsule wall thickness and surface area.

In tablet formulations, ethylcellulose may additionally be employed as a binder, the ethylcellulose being blended dry or wet-granulated with a solvent such as ethanol (95%). Ethylcellulose produces hard tablets with low friability, although they may demonstrate poor dissolution.

Ethylcellulose has also been used as an agent for delivering therapeutic agents from oral (e.g. dental) appliances.(23)

In topical formulations, ethylcellulose is used as a thickening agent in creams, lotions, or gels, provided an appropriate solvent is used.(24) Ethylcellulose has been studied as a stabilizer for emulsions.(25)

Ethylcellulose is additionally used in cosmetics and food products.

Table I: Uses of ethylcellulose.

Use	Concentration (%)
Microencapsulation	10.0–20.0
Sustained-release tablet coating	3.0–20.0
Tablet coating	1.0–3.0
Tablet granulation	1.0–3.0

8 Description

Ethylcellulose is a tasteless, free-flowing, white to light tan-colored powder.

9 Pharmacopeial Specifications

See Tables II and III.

10 Typical Properties

Density (bulk): 0.4 g/cm^3
Glass transition temperature: 129–133°C(26)
Moisture content: ethylcellulose absorbs very little water from humid air or during immersion, and that small amount evaporates readily.(27,28) *See also* Figure 1.

Table II: Pharmacopeial specifications for ethylcellulose.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Acidity or alkalinity	+	—
Viscosity	*See* Table III	*See* Table III
Loss on drying	⩽3.0%	⩽3.0%
Residue on ignition	—	⩽0.4%
Sulfated ash	⩽0.5%	—
Lead	—	⩽10 ppm
Heavy metals	⩽20 ppm	⩽20 µg/g
Acetaldehyde	⩽100 ppm	—
Chlorides	⩽0.1%	—
Organic volatile impurities	—	+
Assay (of ethoxyl groups)	44.0–51.0%	44.0–51.0%

Table III: Pharmacopeial specifications for ethylcellulose viscosity.

Test	PhEur 2005	USPNF 23
Nominal viscosity		
>6 mPa s	75–140% of that stated for its nominal viscosity	75–140% of that stated for its nominal viscosity
6–10 mPa s	80–120% of that stated for its nominal viscosity	80–120% of that stated for its nominal viscosity
⩽10 mPa s	80–120% of that stated for its nominal viscosity	90–110% of that stated for its nominal viscosity

Particle size distribution: *see* Table IV; *see also* Figures 2 and 3.

Solubility: ethylcellulose is practically insoluble in glycerin, propylene glycol, and water. Ethylcellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%). Ethylcellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene.

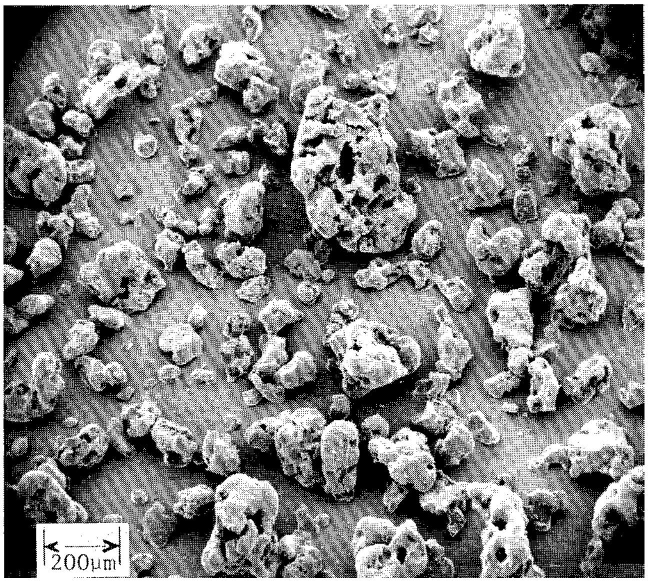
Specific gravity: 1.12–1.15 g/cm^3

Viscosity: the viscosity of ethylcellulose is measured typically at 25°C using 5% w/v ethylcellulose dissolved in a solvent blend of 80% toluene : 20% ethanol (w/w). Grades of ethylcellulose with various viscosities are commercially available; *see* Table IV. They may be used to produce 5% w/v solutions in organic solvent blends with viscosities nominally ranging from 7 to 100 mPa s (7–100 cP). Specific ethylcellulose grades, or blends of different grades, may be used to obtain solutions of a desired viscosity. Solutions of higher viscosity tend to be composed of longer polymer chains and produce strong and durable films.

The viscosity of an ethylcellulose solution increases with an increase in ethylcellulose concentration; e.g. the viscosity of a 5% w/v solution of *Ethocel Standard 4 Premium* is 4 mPa s (4 cP) and of a 25% w/v solution of the same ethylcellulose grade is 850 mPa s (850 cP). Solutions with a lower viscosity may be obtained by incorporating a higher percentage (30–40%) of a low-molecular-weight aliphatic alcohol such as ethanol, butanol, propan-2-ol, or *n*-butanol with toluene. The viscosity of such solutions depends almost entirely on the alcohol content and is independent of toluene.

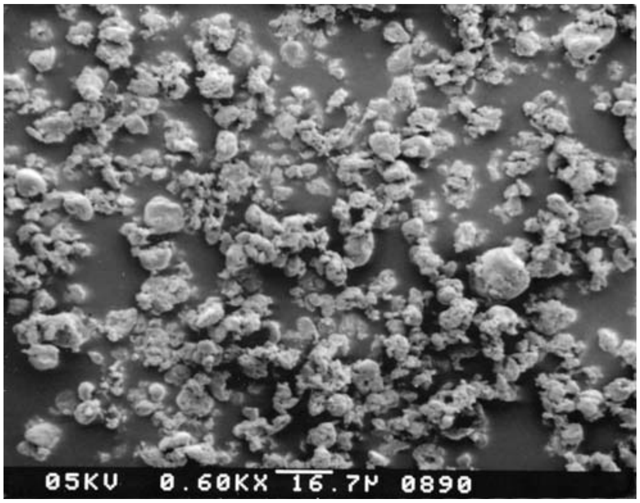
SEM: 1

Excipient: Ethylcellulose
Manufacturer: Hercules Ltd.
Lot No.: 57911
Magnfication: 60×
Voltage: 10 kV

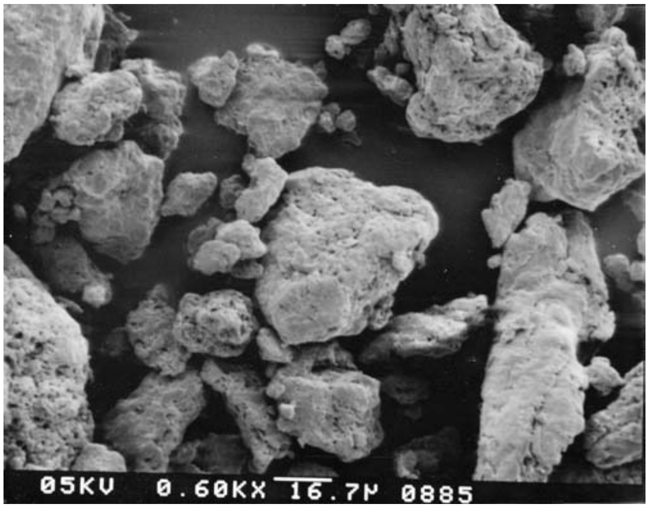


SEM: 2

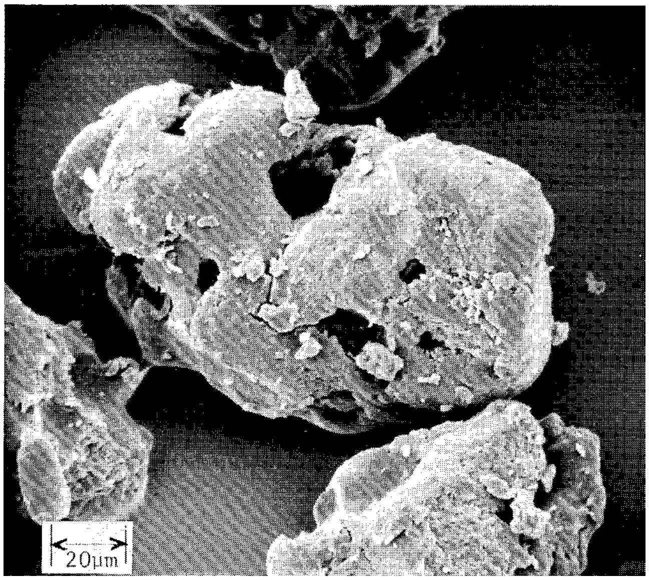
Excipient: Ethylcellulose 10 mPa s (10 cP) fine powder
Manufacturer: Dow Chemical Co.
Magnification: 600×
Voltage: 5 kV



SEM: 3
Excipient: Ethylcellulose 100 mPa s (100 cP) fine powder
Manufacturer: Dow Chemical Co.
Magnification: 600×
Voltage: 5 kV



SEM: 4
Excipient: Ethylcellulose
Manufacturer: Hercules Ltd.
Lot No.: 57911
Magnfication: 600×
Voltage: 10 kV



In addition, nonpharmaceutical grades of ethylcellulose that differ in their ethoxyl content and degree of polymerization are available.

Table IV: Summary of ethylcellulose grades, suppliers, viscosity, and particle size.

Grade	Supplier	Solution viscosity (mPa s)	Mean particle size (µm)
Ethocel Std 4 Premium	Dow Chemical	3.0–5.5	—
N-7	Aqualon	5.6–8.0	—
Ethocel Std 7FP Premium	Dow Chemical	6.0–8.0	5.0–15.0
Ethocel Std 7 Premium	Dow Chemical	6.0–8.0	310.0
T-10	Aqualon	8.0–11.0	—
N-10	Aqualon	8.0–11.0	—
Ethocel Std 10FP Premium	Dow Chemical	9.0–11.0	3.0–15.0
Ethocel Std 10P Premium	Dow Chemical	9.0–11.0	375.0
N-14	Aqualon	12.0–16.0	—
Ethocel Std 20P Premium	Dow Chemical	18.0–22.0	—
N-22	Aqualon	18.0–24.0	—
Ethocel Std 45P Premium	Dow Chemical	41.0–49.0	—
N-50	Aqualon	40.0–52.0	—
N-100	Aqualon	80.0–105.0	—
Ethocel Std 100FP Premium	Dow Chemical	90.0–110.0	30.0–60.0
Ethocel Std 100P Premium	Dow Chemical	90.0–110.0	465.0

11 Stability and Storage Conditions

Ethylcellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters.

Ethylcellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by the use of antioxidant and chemical additives that absorb light in the 230–340 nm range.

Ethylcellulose should be stored at a temperature not exceeding 32°C (90°F) in a dry area away from all sources of heat. It should not be stored next to peroxides or other oxidizing agents.

12 Incompatibilities

Incompatible with paraffin wax and microcrystalline wax.

13 Method of Manufacture

Ethylcellulose is prepared by treating purified cellulose (sourced from chemical-grade cotton linters and wood pulp) with an alkaline solution, followed by ethylation of the alkali cellulose with chloroethane as shown below, where R represents the cellulose radical:

$$\mathrm{RONa} + \mathrm{C_2H_5Cl} \rightarrow \mathrm{ROC_2H_5} + \mathrm{NaCl}$$

The manner in which the ethyl group is added to cellulose can be described by the degree of substitution (DS). The DS designates the average number of hydroxyl positions on the anhydroglucose unit that have been reacted with ethyl chloride. Since each anhydroglucose unit of the cellulose molecule has three hydroxyl groups, the maximum value for DS is three.

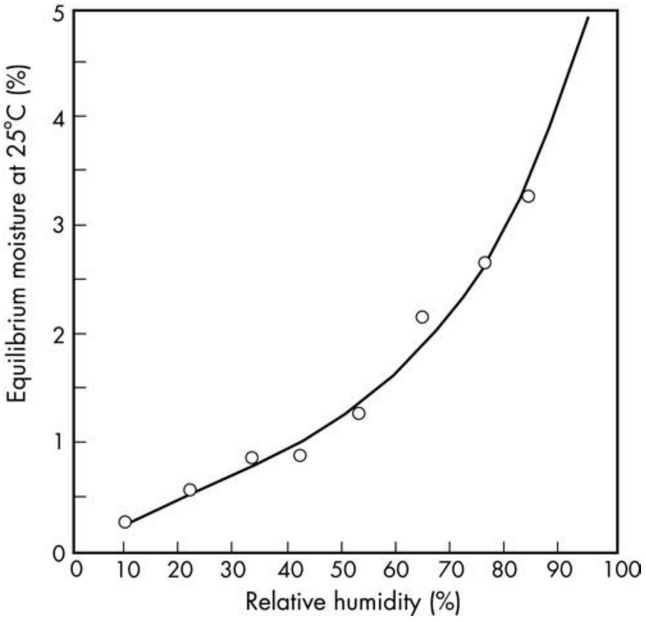


Figure 1: Equilibrium moisture content of ethylcellulose.

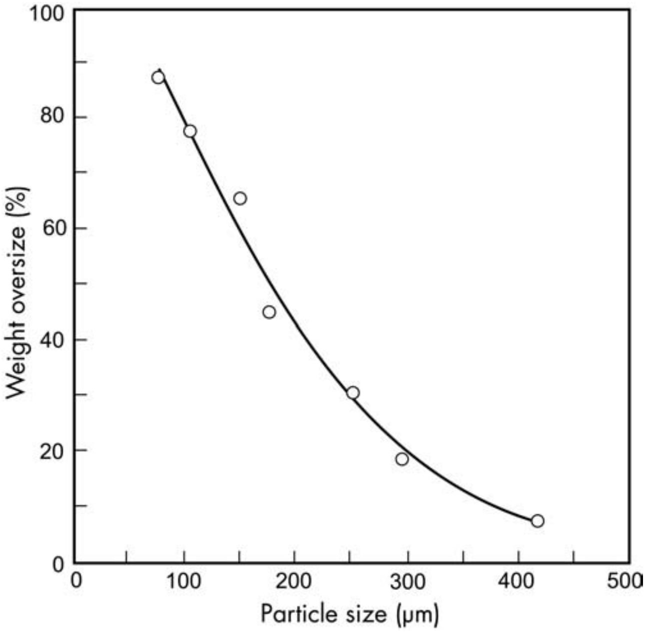


Figure 2: Particle size distribution of ethylcellulose.

14 Safety

Ethylcellulose is widely used in oral and topical pharmaceutical formulations. It is also used in food products. Ethylcellulose is not metabolized following oral consumption and is therefore a noncalorific substance. Because ethylcellulose is not metabolized it is not recommended for parenteral products; parenteral use may be harmful to the kidneys.

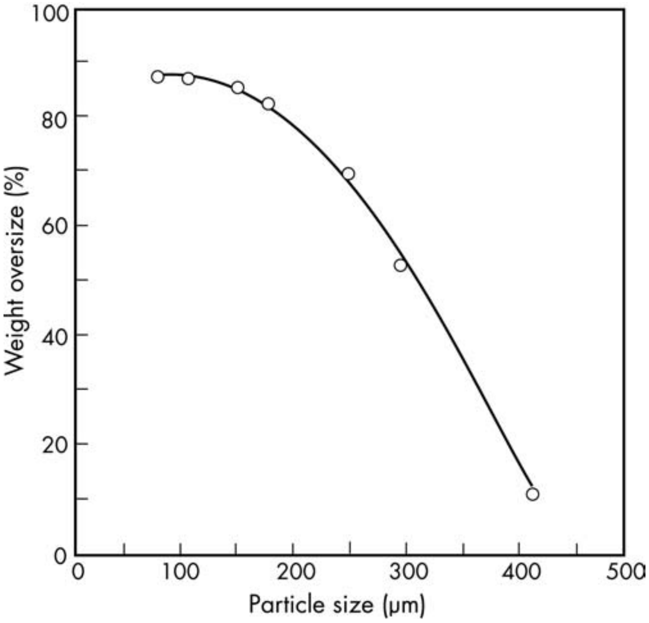


Figure 3: Particle size distribution of ethylcellulose (*Ethocel*).

Ethylcellulose is generally regarded as a nontoxic, nonallergenic, and nonirritating material.

As ethylcellulose is not considered to be a health hazard, the WHO has not specified an acceptable daily intake.(29)

LD_{50} (rabbit, skin): >5 g/kg(30)
LD_{50} (rat, oral): >5 g/kg

15 Handling Precautions

It is important to prevent fine dust clouds of ethylcellulose from reaching potentially explosive levels in the air. Ethylcellulose is combustible. Ethylcellulose powder may be an irritant to the eyes and eye protection should be worn.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules, suspensions and tablets; topical emulsions and vaginal preparations). Included in nonparenteral medicines licensed in Europe. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Hydroxyethyl cellulose; hydroxyethylmethyl cellulose; methylcellulose.

18 Comments

Ethylcellulose is compatible with the following plasticizers: dibutyl phthalate; diethyl phthalate; dibutyl sebacate; triethyl citrate; tributyl citrate; acetylated monoglyceride; acetyl tributyl citrate; triacetin; dimethyl phthalate; benzyl benzoate; butyl and glycol esters of fatty acids; refined mineral oils; oleic acid; stearic acid; ethyl alcohol; stearyl alcohol; castor oil; corn oil; and camphor.

Ethylcellulose has also been used as a backing membrane on mucoadhesive patches intended for buccal administration. The membrane had high tensile strength, and provided excellent unidirectional drug flow.(31) Studies have also suggested ethylcellulose for use in floating microparticles based on low-density foam powder, for gastroretentive drug delivery systems.(32)

A specification for ethylcellulose is contained in the Food Chemicals Codex (FCC).

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21 Authors

TC Dahl.

22 Date of Revision

19 August 2005.

Ethylene Glycol Palmitostearate

1 Nonproprietary Names

BP: Ethylene glycol monopalmitostearate
PhEur: Ethyleneglycoli monopalmitostearas

2 Synonyms

—

3 Chemical Name and CAS Registry Number

Ethylene glycol palmitostearate

See Sections 8 and 17.

4 Empirical Formula and Molecular Weight

See Section 8.

5 Structural Formula

See Section 8.

6 Functional Category

Emollient; emulsifying agent; stabilizing agent.

7 Applications in Pharmaceutical Formulation or Technology

Ethylene glycol palmitostearate is used as a stabilizer for water-in-oil emulsions, although it has poor emulsifying properties. It has emollient properties and is also used as an opacifying, thickening, and dispersing agent.

In cosmetics, ethylene glycol palmitostearate is used as a 'fatty body' for lipsticks, as a pearling agent in opalescent and cream shampoos, and as an additive for tanning lubricants.

8 Description

The PhEur 2005 describes ethylene glycol palmitostearate as a mixture of ethylene glycol monoesters and diesters of stearic and palmitic acids, produced from the condensation of ethylene glycol and stearic acid 50, of vegetable or animal origin.

Ethylene glycol palmitostearate occurs as a white or almost white waxy solid.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for ethylene glycol palmitostearate.

Test	PhEur 2005
Characters	+
Identification	+
Melting point	54–60°C
Acid value	⩽3.0
Iodine value	⩽3.0
Saponification value	170–195
Composition of fatty acids	
Stearic acid	40.0–60.0%
Total of palmitic acid and stearic acid	⩾90.0%
Free ethylene glycol	⩽5.0%
Total ash	⩽0.1%

10 Typical Properties

Melting point: 54–60°C

Solubility: soluble in acetone and hot ethanol (95%); practically insoluble in water.

11 Stability and Storage Conditions

Ethylene glycol palmitostearate should be stored in a cool, dark place, protected from light.

12 Incompatibilities

—

13 Method of Manufacture

Ethylene glycol palmitostearate is produced from the condensation of ethylene glycol with stearic acid 50 of vegetable or animal origin.

14 Safety

Ethylene glycol palmitostearate is mainly used in cosmetics and topical pharmaceutical formulations, where it is generally regarded as a relatively nontoxic and nonirritant material.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Included in nonparenteral medicines licensed in Europe.

17 Related Substances

Diethylene glycol monopalmitostearate; ethylene glycol monopalmitate; ethylene glycol monostearate; glyceryl monostearate; glyceryl palmitostearate.

Diethylene glycol monopalmitostearate

Synonyms: diethyleneglycoli monopalmitostearas; diethylene glycol palmitostearate.

Description: the PhEur 2005 describes diethylene glycol monopalmitostearate as a mixture of diethylene glycol monoesters and diesters of stearic and palmitic acids. It contains not less than 45.0% of monoesters produced from the condensation of diethylene glycol and stearic acid 50 of vegetable or animal origin. Diethylene glycol monopalmitostearate occurs as a white or almost white waxy solid.

Acid value: $\leqslant$4.0

Iodine value: $\leqslant$3.0

Melting point: 43–50°C

Saponification value: 150–170

Solubility: soluble in acetone and hot ethanol (95%); practically insoluble in water.

Ethylene glycol monopalmitate

CAS number: [4219-49-2]

Ethylene glycol monostearate

Synonyms: ethylene glycol stearate; ethylene glycoli monostearas; ethyleni glycoli stearas; 2-hydroxyethyl ester stearic acid; *Monestriol EN-A*; *Monthyle*.

CAS number: [111-60-4]

Empirical formula: $C_{20}H_{40}O_3$

Molecular weight: 328.60

Description: occurs as pale yellow flakes.

Melting point: 57–63°C

Safety: LD_{50} (mouse, IP): 0.20 g/kg(1)

18 Comments

—

19 Specific References

1 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 1669.

20 General References

Sweetman S, ed. *Martindale: The Complete Drug Reference*. 34th edn. London: Pharmaceutical Press, 2005: 1411.

21 Authors

SC Owen, PJ Sheskey.

22 Date of Revision

12 August 2005.

Ethylene Vinyl Acetate

1 Nonproprietary Names

None adopted.

2 Synonyms

Acetic acid, ethylene ester polymer with ethane; *CoTran*; ethylene/vinyl acetate copolymer; EVA; EVA copolymer; EVM; poly (ethylene-co-vinyl acetate); VA/ethylene copolymer; vinyl acetate/ethylene copolymer.

3 Chemical Name and CAS Registry Number

Ethylene vinyl acetate copolymer [24937-78-8]

4 Empirical Formula and Molecular Weight

$(CH_2CH_2)_x[CH_2CH(CO_2CH_3)]_y$

See Section 5.

5 Structural Formula

Ethylene vinyl acetate copolymer is a random copolymer of ethylene and vinyl acetate.

6 Functional Category

Membrane; transdermal backing.

7 Applications in Pharmaceutical Formulation or Technology

Ethylene vinyl acetate copolymers are used as membranes and backings in laminated transdermal drug delivery systems. They can also be incorporated as components in backings in transdermal systems. Ethylene vinyl acetate copolymers have been shown to be an effective matrix and membrane for the controlled delivery of atenolol(1,2) triprolidine,(3,4) and furosemide.(5) The system for the controlled release of atenolol can be further developed using ethylene vinyl acetate copolymers and plasticizers.(1)

8 Description

Ethylene vinyl acetate is available as white waxy solids in pellet or powder form. Films are translucent.

9 Pharmacopeial Specifications

—

10 Typical Properties

Density: 0.92–0.94 g/cm^3

Flash point: 260°C

Melting point: 75–102°C depending on polymer ratios.

Moisture vapor transmission rate: *see* Table I.

Thickness: *see* Table I.

Vinyl acetate content: *see* Table I.

Table I: Characteristics of different *CoTran* (3M Drug Delivery Systems) film grades.

Grade	Vinyl acetate (%)	Thickness (μm)	Moisture vapor transmission rate (g/m^2/24 h)
CoTran 9706	9	101.6	26.4
CoTran 9715	19	76.2	64.8
CoTran 9716	19	101.6	48.6

11 Stability and Storage Conditions

Ethylene vinyl acetate copolymers are stable under normal conditions and should be stored in a cool, dry place. Films of ethylene vinyl acetate copolymers should be stored at 0–30°C and less than 75% relative humidity.

12 Incompatibilities

Ethylene vinyl acetate is incompatible with strong oxidizing agents and bases.

13 Method of Manufacture

Various molecular weights of random ethylene vinyl acetate copolymers can be obtained by high-pressure radical polymerization, bulk continuous polymerization, or solution polymerization.

14 Safety

Ethylene vinyl acetate is mainly used in topical pharmaceutical applications as a membrane or film backing. Generally it is regarded as a relatively nontoxic and nonirritant excipient.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Ethylene vinyl acetate powder may form an explosive mixture with air.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (intrauterine suppository; ophthalmic preparations; periodontal film; transdermal film). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

—

18 Comments

Ethylene vinyl acetate copolymers have a wide variety of industrial uses. Properties of ethylene vinyl acetate copolymer films in terms of oxygen and moisture transfer rate are related to the vinyl acetate content and thickness. Higher levels of vinyl acetate result in increased lipophilicity, increased oxygen and moisture vapor permeability, and increased clarity, flexibility, toughness, and solvent solubility.

19 Specific References

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S Edge, PM Young.

22 Date of Revision

16 August 2005.

Ethylparaben

1 Nonproprietary Names

BP: Ethyl hydroxybenzoate
JP: Ethyl parahydroxybenzoate
PhEur: Ethylis parahydroxybenzoas
USPNF: Ethylparaben

2 Synonyms

E214; ethyl *p*-hydroxybenzoate; *Ethyl parasept*; 4-hydroxybenzoic acid ethyl ester; *Solbrol A*; *Tegosept E.*

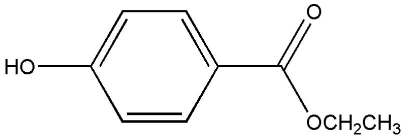
3 Chemical Name and CAS Registry Number

Ethyl-4-hydroxybenzoate [120-47-8]

4 Empirical Formula and Molecular Weight

$C_9H_{10}O_3$ 166.18

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

Ethylparaben is widely used as an antimicrobial preservative in cosmetics,(1) food products, and pharmaceutical formulations.

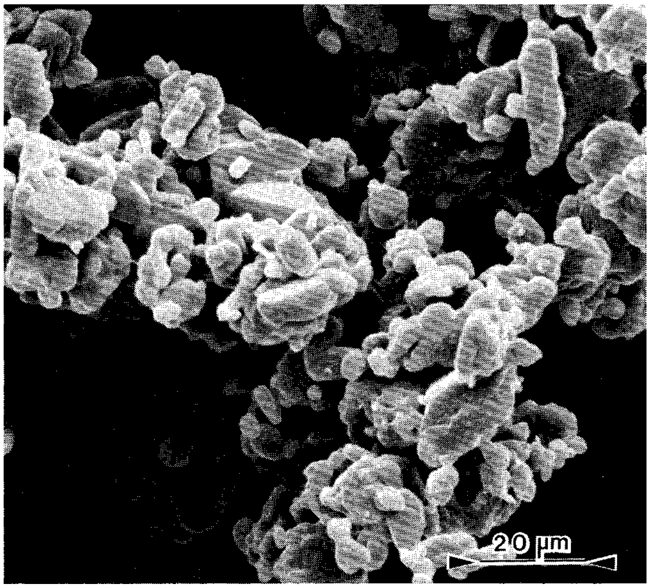
It may be used either alone or in combination with other paraben esters or with other antimicrobial agents. In cosmetics it is one of the most frequently used preservatives.

The parabens are effective over a wide pH range and have a broad spectrum of antimicrobial activity, although they are most effective against yeasts and molds; *see* Section 10.

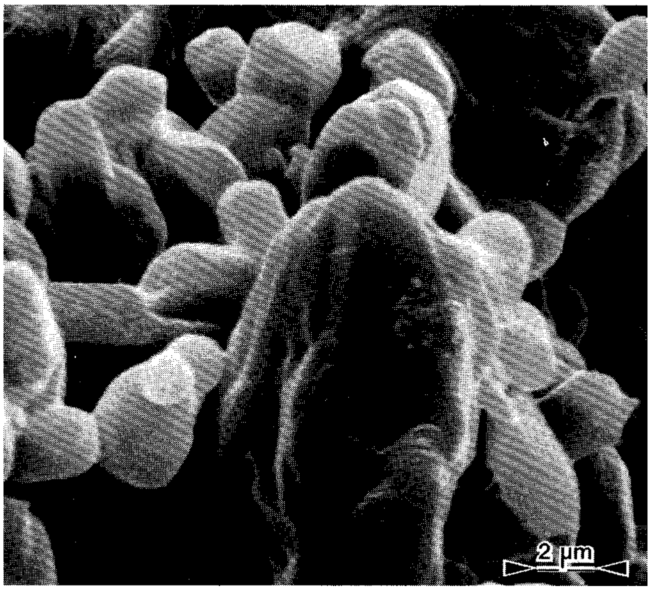
Owing to the poor solubility of the parabens, paraben salts, particularly the sodium salt, are frequently used. However, this may cause the pH of poorly buffered formulations to become more alkaline.

See Methylparaben for further information.

SEM: 1
Excipient: Ethylparaben
Magnification: 600×



SEM: 2
Excipient: Ethylparaben
Magnification: 3000×



8 Description

Ethylparaben occurs as a white, odorless or almost odorless, crystalline powder.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for ethylparaben.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Appearance of solution	—	+	—
Characters	—	+	—
Chloride	⩽0.035%	—	—
Heavy metals	⩽20 ppm	—	—
Acidity	—	+	+
Loss on drying	⩽0.5%	—	⩽0.5%
Melting range	116–118°C	—	115–118°C
Organic volatile impurities	—	—	+
Readily carbonizable substances	+	—	—
Related substances	—	+	+
Residue on ignition	⩽0.1%	⩽0.1%	⩽0.05%
Sulfate	⩽0.024%	—	—
Parahydroxybenzoic acid	+	—	—
Assay (dried basis)	⩾99.0%	98.0–102.0%	99.0–100.5%

10 Typical Properties

Antimicrobial activity: ethylparaben exhibits antimicrobial activity from pH 4–8. Preservative efficacy decreases with increasing pH owing to the formation of the phenolate anion. Parabens are more active against yeasts and molds than against bacteria. They are also more active against Gram-positive than against Gram-negative bacteria.

The activity of the parabens increases with increasing chain length of the alkyl moiety, but solubility decreases. Activity may be improved by using combinations of parabens since synergistic effects occur. Ethylparaben is commonly used with methylparaben and propylparaben in oral and topical formulations (such mixtures are commercially available; for example, *Nipasept* (Nipa Laboratories Inc.). Activity has also been reported to be improved by the addition of other excipients; *see* Methylparaben for further information.

See Table II for minimum inhibitory concentrations of ethylparaben.(2)

Boiling point: 297–298°C with decomposition.

Melting point: 115–118°C

Partition coefficient: the values for different vegetable oils vary considerably and are affected by the purity of the oil; *see* Table III.(3)

Solubility: *see* Table IV.

11 Stability and Storage Conditions

Aqueous ethylparaben solutions at pH 3–6 can be sterilized by autoclaving, without decomposition.(4) At pH 3–6, aqueous solutions are stable (less than 10% decomposition) for up to about 4 years at room temperature, while solutions at pH 8 or above are subject to rapid hydrolysis (10% or more after about 60 days at room temperature).(5)

Ethylparaben should be stored in a well-closed container in a cool, dry place.

Table II: Minimum inhibitory concentrations (MICs) for ethylparaben in aqueous solution.(2)

Microorganism	MIC (μg/mL)
Aerobacter aerogenes ATCC 8308	1200
Aspergillus niger ATCC 9642	500
Aspergillus niger ATCC 10254	400
Bacillus cereus var. *mycoides* ATCC 6462	1000
Bacillus subtilis ATCC 6633	1000
Candida albicans ATCC 10231	500
Enterobacter cloacae ATCC 23355	1000
Escherichia coli ATCC 8739	1000
Escherichia coli ATCC 9637	1000
Klebsiella pneumoniae ATCC 8308	500
Penicillium chrysogenum ATCC 9480	250
Penicillium digitatum ATCC 10030	250
Proteus vulgaris ATCC 13315	500
Pseudomonas aeruginosa ATCC 9027	>2000
Pseudomonas aeruginosa ATCC 15442	>2000
Pseudomonas stutzeri	1000
Rhizopus nigricans ATCC 6227A	250
Saccharomyces cerevisiae ATCC 9763	500
Salmonella typhosa ATCC 6539	1000
Serratia marcescens ATCC 8100	1000
Staphylococcus aureus ATCC 6538P	1000
Staphylococcus epidermidis ATCC 12228	1000
Trichophyton mentagrophytes	125

Table III: Partition coefficients for ethylparaben in vegetable oil and water.(3)

Solvent	Partition coefficient oil : water
Corn oil	14.0
Mineral oil	0.13
Peanut oil	16.1
Soybean oil	18.8

Table IV: Solubility of ethylparaben in various solvents.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	Freely soluble
Ethanol	1 in 1.4
Ethanol (95%)	1 in 2
Ether	1 in 3.5
Glycerin	1 in 200
Methanol	1 in 0.9
Mineral oil	1 in 4000
Peanut oil	1 in 100
Propylene glycol	1 in 4
Water	1 in 1250 at 15°C
	1 in 910
	1 in 120 at 80°C

12 Incompatibilities

The antimicrobial properties of ethylparaben are considerably reduced in the presence of nonionic surfactants as a result of micellization.(6) Absorption of ethylparaben by plastics has not been reported, although it appears probable given the behavior of other parabens. Ethylparaben is coabsorbed on silica in the presence of ethoxylated phenols.(7) Yellow iron oxide, ultramarine blue, and aluminum silicate extensively absorb ethylparaben in simple aqueous systems, thus reducing preservative efficacy.(8,9)

Ethylparaben is discolored in the presence of iron and is subject to hydrolysis by weak alkalis and strong acids.

See also Methylparaben.

13 Method of Manufacture

Ethylparaben is prepared by the esterification of *p*-hydroxybenzoic acid with ethanol (95%).

14 Safety

Ethylparaben and other parabens are widely used as antimicrobial preservatives in cosmetics, food products, and oral and topical pharmaceutical formulations.

Systemically, no adverse reactions to parabens have been reported, although they have been associated with hypersensitivity reactions. Parabens, *in vivo*, have also been reported to exhibit estrogenic responses in fish.(10) The WHO has set an estimated total acceptable daily intake for methyl-, ethyl-, and propylparabens at up to 10 mg/kg body-weight.(11)

LD_{50} (mouse, IP): 0.52 g/kg(12)
LD_{50} (mouse, oral): 3.0 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Ethylparaben may be irritant to the skin, eyes, and mucous membranes and should be handled in a well ventilated environment. Eye protection, gloves, and a dust mask or respirator are recommended.

16 Regulatory Status

Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral, otic, and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Butylparaben; ethylparaben potassium; ethylparaben sodium; methylparaben; propylparaben.

Ethylparaben potassium

Empirical formula: $C_9H_9KO_3$
Molecular weight: 204.28
CAS number: [36547-19-9]
Synonyms: ethyl 4-hydroxybenzoate potassium salt; potassium ethyl hydroxybenzoate.

Ethylparaben sodium

Empirical formula: $C_9H_9NaO_3$
Molecular weight: 188.17
CAS number: [35285-68-8]
Synonyms: E215; ethyl 4-hydroxybenzoate sodium salt; sodium ethyl hydroxybenzoate.

18 Comments

See Methylparaben for further information.

The EINECS number for ethylparaben is 204-399-4.

19 Specific References

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10 Pedersen KL, Pedersen SN, Christiansen LB, *et al*. The preservatives ethyl-, propyl-, and butylparaben are oestrogenic in an *in vivo* fish assay. *Pharmacol Toxicol* 2000; **86**(3): 110–113.
11 FAO/WHO. Toxicological evaluation of certain food additives with a review of general principles and of specifications. Seventeenth report of the FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1974; No. 539.
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20 General References

Golightly LK, Smolinske SS, Bennett ML, *et al*. Pharmaceutical excipients: adverse effects associated with inactive ingredients in drug products (part I). *Med Toxicol* 1988; **3**: 128–165.

21 Authors

R Johnson, R Steer.

22 Date of Revision

23 August 2005.

Fructose

1 Nonproprietary Names

BP: Fructose
JP: Fructose
PhEur: Fructosum
USP: Fructose

2 Synonyms

Advantose FS 95; *Fructamyl*; D-(–)-fructopyranose; β-D-fructose; fruit sugar; *Krystar*; laevulose; levulose.

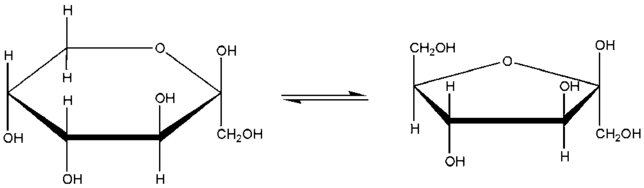
3 Chemical Name and CAS Registry Number

D-Fructose [57-48-7]

4 Empirical Formula and Molecular Weight

$C_6H_{12}O_6$ 180.16

5 Structural Formula



Pyranose form

Furanose form

See Section 18.

6 Functional Category

Dissolution enhancer; flavor enhancer; sweetening agent; tablet diluent.

7 Applications in Pharmaceutical Formulation or Technology

Fructose is used in tablets, syrups, and solutions as a flavoring and sweetening agent.

The sweetness-response profile of fructose is perceived in the mouth more rapidly than that of sucrose and dextrose, which may account for the ability of fructose to enhance syrup or tablet fruit flavors and mask certain unpleasant vitamin or mineral 'off-flavors'.

The increased solubility of fructose in comparison to sucrose is advantageous in syrup or solution formulations that must be refrigerated, since settling or crystallization of ingredients is retarded. Similarly, the greater solubility and hygroscopicity of fructose over sucrose and dextrose helps to avoid 'cap-locking' (sugar crystallization around the bottle cap) in elixir preparations. Fructose also has greater solubility in ethanol (95%) and is therefore used to sweeten alcoholic formulations.

The water activity of a sweetener influences product microbial stability and freshness. Fructose has a lower water activity and a higher osmotic pressure than sucrose. Syrup formulations may be made at lower dry-substance levels than sugar syrups without compromising shelf-life stability. It may be necessary to include a thickener or gelling agent to match the texture or viscosity of the sugar-equivalent formulation.

Fructose is sweeter than the sugar alcohols mannitol and sorbitol, which are commonly used as tableting excipients. Although fructose is effective at masking unpleasant flavors in tablet formulations, tablets of satisfactory hardness and friability can only be produced by direct compression if tablet presses are operated at relatively slow speeds. However, by the combination of crystalline fructose with tablet-grade sorbitol in a 3 : 1 ratio, satisfactory direct-compression characteristics can be achieved. A directly compressible grade of fructose, containing a small amount of starch (*Advantose FS 95*, SPI Pharma) is also commercially available. Pregranulation of fructose with 3.5% povidone also produces a satisfactory tablet excipient.(1) The added sweetness of fructose may also be used to advantage by coating the surface of chewable tablets, lozenges, or medicinal gums with powdered fructose.

The coprecipitation of fructose with hydrophobic drugs such as digoxin has been shown to enhance the dissolution profile of such drugs. Fructose apparently acts as a water-soluble carrier upon coprecipitation, thereby allowing hydrophobic drugs to be more readily wetted.(2)

8 Description

Fructose occurs as odorless, colorless crystals or a white crystalline powder with a very sweet taste.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acidity/alkalinity: pH = 5.35 (9% w/v aqueous solution)
Angle of repose: 38.8° for *Advantose FS 95*
Density: 1.58 g/cm^3. *See also* Table II.
Heat of combustion: 15.3 kJ/g (3.66 kcal/g)
Heat of solution: 50.2 kJ/g (12 kcal/g)
Hygroscopicity: at 25°C and relative humidities above approximately 60%, fructose absorbs significant amounts of moisture; *see* Figure 1.
Melting point: ≈102–105°C (with decomposition)
Osmolarity: a 5.05% w/v aqueous solution is isoosmotic with serum.
Particle size distribution: the average particle size of standard-grade crystalline fructose is 170–450 μm. The average particle size of powdered fructose is 25–40 μm.
Refractive index: *see* Table II.
Solubility: *see* Table III.
Specific rotation $[\alpha]_D^{20}$: −132° to −92° (2% w/v aqueous solution). Note that fructose shows rapid and anomalous mutarotation involving pyranose–furanose interconversion.

The final value may be obtained in the presence of hydroxide ions. *See also* Section 18.

Viscosity (dynamic): *see* Table II.

Table I: Pharmacopeial specifications for fructose.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	—	+	—
Color of solution	+	+	+
Acidity	+	+	+
pH	4.0–6.5	—	—
Specific optical rotation	—	−91.0° to −93.5°	—
Foreign sugars	—	+	—
Loss on drying	$\leqslant$0.5%	—	$\leqslant$0.5%
Residue on ignition	$\leqslant$0.1%	$\leqslant$0.1%	$\leqslant$0.5%
Chloride	$\leqslant$0.018%	—	$\leqslant$0.018%
Sulfate	$\leqslant$0.024%	—	$\leqslant$0.025%
Sulfite	+	—	—
Water	—	$\leqslant$0.5%	—
Arsenic	$\leqslant$1.3 ppm	—	$\leqslant$1 ppm
Barium	—	+	—
Calcium and magnesium (as calcium)	+	—	$\leqslant$0.005%
Lead	—	$\leqslant$0.5 ppm	—
Heavy metals	$\leqslant$4 ppm	—	$\leqslant$5 ppm
Hydroxymethylfurfural	+	+	+
Assay (dried basis)	$\geqslant$98.0%	—	98.0–102.0%

Table II: Physical properties of aqueous fructose solutions at 20°C.

Concentration of aqueous fructose solution (% w/w)	Density (g/cm^3)	Refractive index	Viscosity, dynamic (mPa s)
10	1.04	1.3477	1.35
20	1.08	1.3633	1.80
30	1.13	1.3804	2.90
40	1.18	1.3986	5.60
50	1.23	1.4393	34.0
60	1.29	1.4853	309.2

Table III: Solubility of fructose.

Solvent	Solubility at 20°C
Ethanol (95%)	1 in 15
Methanol	1 in 14
Water	1 in 0.3

11 Stability and Storage Conditions

Fructose is hygroscopic and absorbs significant amounts of moisture at relative humidities greater than 60%. Goods stored in the original sealed packaging at temperatures below 25°C and a relative humidity of less than 60% can be expected to retain stability for at least 12 months.

Aqueous solutions are most stable at pH 3–4 and temperatures of 4–70°C; they may be sterilized by autoclaving.

12 Incompatibilities

Incompatible with strong acids or alkalis, forming a brown coloration. In the aldehyde form, fructose can react with amines, amino acids, peptides, and proteins. Fructose may cause browning of tablets containing amines.

13 Method of Manufacture

Fructose, a monosaccharide sugar, occurs naturally in honey and a large number of fruits. It may be prepared from inulin, dextrose, or sucrose by a number of methods. Commercially, fructose is mainly manufactured by crystallization from high-fructose syrup derived from hydrolyzed and isomerized cereal starch or cane and beet sugar.

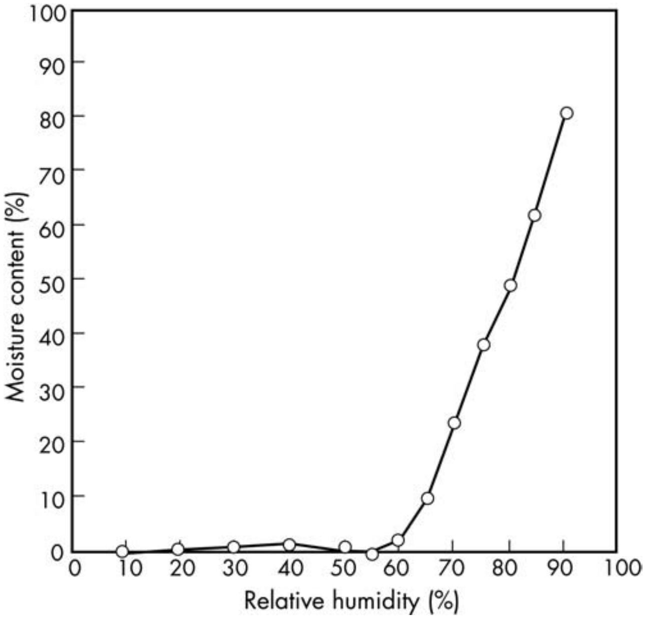


Figure 1: Equilibrium moisture content of fructose at 25°C.

14 Safety

Although it is absorbed more slowly than dextrose from the gastrointestinal tract, fructose is metabolized more rapidly. Metabolism of fructose occurs mainly in the liver, where it is converted partially to dextrose and the metabolites lactic acid and pyruvic acid. Entry into the liver and subsequent phosphorylation is insulin-independent. Further metabolism occurs by way of a variety of metabolic pathways. In healthy and well regulated diabetics, glycogenesis (glucose stored as glycogen) predominates.

Excessive oral fructose consumption (>75 g daily) in the absence of dietary dextrose in any form (e.g., sucrose, starch, dextrin, etc.) may cause malabsorption in susceptible individuals, which may result in flatulence, abdominal pain, and diarrhea. Except in patients with hereditary fructose intolerance,(3,4) there is no evidence to indicate that oral fructose intake at current levels is a risk factor in any particular disease, other than dental caries.(5)

See also Section 18.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Fructose may be irritant to the eyes. Eye protection and gloves are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral solutions and suspensions; rectal preparations). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Dextrose; high-fructose syrup; liquid fructose; powdered fructose; sucrose.

High-fructose syrup

Comments: a syrup most commonly containing 42% or 55% fructose, with the remainder consisting of dextrose and small amounts of oligosaccharides. It is a colorless, odorless, highly viscous syrup with a sweet taste.

Liquid fructose

Comments: a syrup containing ≥99.5% fructose, made by solubilizing crystalline fructose in water. It is a colorless, odorless, highly viscous syrup with a sweet taste.

Powdered fructose

Comments: finely ground crystalline fructose containing ≤2% silicon dioxide as a glidant.

18 Comments

Fructose can occur in both the furanose and pyranose forms. Fructose present in natural products occurs in the furanose form, while that produced by crystallization occurs in the pyranose form. An aqueous solution at 20°C contains about 20% of the furanose form.

Although fructose has been proposed for use in the diabetic diet, it is not regarded as a suitable source of carbohydrate, although it does have value as a sweetening agent.(6) The British Diabetic Association has recommended that intake of fructose be limited to 25 g daily.(7)

Fructose has been used as an alternative to dextrose in parenteral nutrition, but its use is not recommended by some because of the risk of lactic acidosis. Although popular in many countries, it has therefore been suggested that the use of intravenous infusions containing fructose and sorbitol should be abandoned.(4,8)

Fructose is the sweetest of all sugars; *see* Table IV. A specification for fructose is contained in the Food Chemicals Codex (FCC).

The EINECS number for fructose is 200-333-3.

Table IV: Relative sweetness of fructose and other sugars.

Sugar	Relative sweetness at 25°C (10% solids)
Fructose	117
Sucrose	100
High fructose syrup-55	99
High fructose syrup-42	92
Dextrose	65

19 Specific References

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20 General References

Muldering KB. Placebo evaluation of selected sugar-based excipients in pharmaceutical and nutraceutical tableting. *Pharm Technol* 2000; **24**(5): 34, 36, 38, 40, 42, 44.

21 Authors

SC Owen.

22 Date of Revision

19 August 2005.

Fumaric Acid

1 Nonproprietary Names

USPNF: Fumaric acid

2 Synonyms

Allomaleic acid; allomalenic acid; boletic acid; butenedioic acid; E297; 1,2-ethenedicarboxylic acid; lichenic acid; *trans*-butenedioic acid; NSC-2752; *trans*-1,2-ethylenedicarboxylic acid; U-1149; USAF EK-P-583.

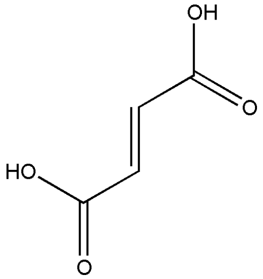
3 Chemical Name and CAS Registry Number

(E)-2-Butenedioic acid [110-17-8]

4 Empirical Formula and Molecular Weight

$C_4H_4O_4$ 116.07

5 Structural Formula



6 Functional Category

Acidulant; antioxidant; flavoring agent; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Fumaric acid is used primarily in liquid pharmaceutical preparations as an acidulant and flavoring agent. Fumaric acid may be included as the acid part of effervescent tablet formulations, although this use is limited as the compound has an extremely low solubility in water. It is also used as a chelating agent which exhibits synergism when used in combination with other true antioxidants.

In the design of novel pelletized formulations manufactured by extrusion–spheronization, fumaric acid was used to aid spheronization, favoring the production of fine pellets.(1) It has also been investigated as an alternative filler to lactose in pellets.(2)

Fumaric acid has been investigated as a lubricant for effervescent tablets(3) and copolymers of fumaric acid and sebacic acid have been investigated as bioadhesive microspheres.(4) It has been used in film-coated pellet formulations as an acidifying agent and also to increase drug solubility.(5)

Fumaric acid is also used as a food additive at concentrations up to 3600 ppm, and as a therapeutic agent in the treatment of psoriasis and other skin disorders.(6)

8 Description

Fumaric acid occurs as white, odorless or nearly odorless, granules or as a crystalline powder that is virtually nonhygroscopic.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for fumaric acid.

Test	USPNF 23
Identification	+
Water	⩽0.5%
Residue on ignition	⩽0.1%
Heavy metals	⩽0.001%
Maleic acid	⩽0.1%
Organic volatile impurities	+
Assay (dried basis)	99.5–100.5%

10 Typical Properties

Acidity/alkalinity:
pH = 2.45 (saturated aqueous solution at 20°C);
pH = 2.58 (0.1% w/v aqueous solution at 25°C);
pH = 2.25 (0.3% w/v aqueous solution at 25°C);
pH = 2.15 (0.5% w/v aqueous solution at 25°C).
Density: 1.635 g/cm^3 at 20°C
Density (bulk): 0.77 g/cm^3
Density (tapped): 0.93 g/cm^3
Dissociation constant:
$pK_{a1} = 3.03$ at 25°C;
$pK_{a2} = 4.54$ at 25°C.
Melting point: 287°C (closed capillary, rapid heating); partial carbonization and formation of maleic anhydride occur at 230°C (open vessel); sublimes at 200°C.
Boiling point: 290°C (sealed tube)
Solubility: *see* Table II.

11 Stability and Storage Conditions

Fumaric acid is stable although it is subject to degradation by both aerobic and anaerobic microorganisms. When heated in sealed vessels with water at 150–170°C it forms (±)-malic acid.

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Fumaric acid undergoes reactions typical of an organic acid.

Table II: Solubility of fumaric acid.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	1 in 58 at 30°C
Benzene	Very slightly soluble
Carbon tetrachloride	Very slightly soluble
Chloroform	Very slightly soluble
Ethanol	1 in 28
Ethanol (95%)	1 in 17 at 30°C
Ether	Slightly soluble 1 in 139 at 25°C
Olive oil	Very slightly soluble
Propylene glycol	1 in 33
Water	1 in 200 1 in 432 at 0°C 1 in 303 at 10°C 1 in 159 at 25°C 1 in 94 at 40°C 1 in 42 at 60°C 1 in 10 at 100°C

13 Method of Manufacture

Commercially, fumaric acid may be prepared from glucose by the action of fungi such as *Rhizopus nigricans*, as a by-product in the manufacture of maleic and phthalic anhydrides, and by the isomerization of maleic acid using heat or a catalyst.

On the laboratory scale, fumaric acid can be prepared by the oxidation of furfural with sodium chlorate in the presence of vanadium pentoxide.

14 Safety

Fumaric acid is used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and nonirritant material. However, acute renal failure and other adverse reactions have occurred following the topical and systemic therapeutic use of fumaric acid and fumaric acid derivatives in the treatment of psoriasis or other skin disorders.(6) Other adverse effects of oral therapy have included disturbances of liver function, gastrointestinal effects, and flushing.(6)

The WHO has stated that the establishment of an estimated acceptable daily intake of fumaric acid or its salts was unnecessary since it is a normal constituent of body tissues.(7)

LD_{50} (mouse, IP): 0.1 g/kg(8)
LD_{50} (rat, oral): 9.3 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Fumaric acid may be irritating to the skin, eyes, and respiratory system and should be handled in a well-ventilated environment. Gloves and eye protection are recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules, suspensions, syrups, extended release and sustained action chewable tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Citric acid monohydrate; malic acid; tartaric acid.

18 Comments

A specification for fumaric acid is contained in the Food Chemical Codex (FCC).

The EINECS number for fumaric acid is 203-743-0.

19 Specific References

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21 Authors

SC Owen.

22 Date of Revision

12 August 2005.

Gelatin

1 Nonproprietary Names

BP: Gelatin
JP: Gelatin
PhEur: Gelatina
USPNF: Gelatin

2 Synonyms

Byco; *Cryogel*; gelatine; *Instagel*; *Solugel*.

3 Chemical Name and CAS Registry Number

Gelatin [9000-70-8]

4 Empirical Formula and Molecular Weight

Gelatin is a generic term for a mixture of purified protein fractions obtained either by partial acid hydrolysis (type A gelatin) or by partial alkaline hydrolysis (type B gelatin) of animal collagen. Gelatin may also be a mixture of both types.

The protein fractions consist almost entirely of amino acids joined together by amide linkages to form linear polymers, varying in molecular weight from 15 000–250 000.

The JP 2001 also includes a monograph for purified gelatin.

5 Structural Formula

See Section 4.

6 Functional Category

Coating agent; film-former; gelling agent; suspending agent; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Gelatin is widely used in a variety of pharmaceutical formulations, including its use as a biodegradable matrix material in an implantable delivery system,(1) although it is most frequently used to form either hard or soft gelatin capsules.(2–4)

Gelatin capsules are unit-dosage forms that are filled with an active drug and are generally designed for oral administration. Although gelatin is poorly soluble in cold water, a gelatin capsule will swell in gastric fluid to rapidly release its contents.

Hard capsules are manufactured in two pieces by dipping stainless steel pins into a gelatin solution, which is distributed evenly around the pin. The gelatin is then set with a blast of chilled air and dried to remove moisture. The capsule halves are then removed, trimmed and filled before they are joined and closed with a tamper-evident seal. The USPNF 23 permits gelatin that is used to produce hard capsules to contain various coloring agents, antimicrobial preservatives, and sodium lauryl sulfate. Manufacturers may also add a hardening agent, such as sucrose, to hard gelatin capsules. Capsules varying in size from 0.13 to 1.37 mL volume are commercially available.

Soft gelatin capsules are formed from an aqueous gelatin solution that contains a plasticizer such as glycerin or sorbitol. Two soft gelatin strips are formed that run between suitable dies. As the dies meet, capsules are formed by injecting the filling material, followed by the capsule halves being sealed together.

Gelatin is also used for the microencapsulation of drugs, where the active drug is sealed inside a microsized capsule or beadlet, which may then be handled as a powder. The first microencapsulated drugs (beadlets) were fish oils and oily vitamins in gelatin beadlets prepared by an emulsion process.

Low-molecular-weight gelatin has been investigated for its ability to enhance the dissolution of orally ingested drugs.(5) Ibuprofen–gelatin micropellets have been prepared for the controlled release of the drug.(6) Other uses of gelatin include the preparation of pastes, pastilles, pessaries, and suppositories. In addition, it is used as a tablet binder and coating agent, and as a viscosity-increasing agent for solutions and semisolids.

Therapeutically, gelatin has been used in the preparation of wound dressings(7) and has been used as a plasma substitute, although anaphylactoid reactions have been reported in the latter application.(8) Absorbable gelatin is available as sterile film, ophthalmic film, sterile sponge, sterile compressed sponge, and sterile powder from sponge. Gelatin sponge has hemostatic properties.

Gelatin is also widely used in food products and photographic emulsions.

8 Description

Gelatin occurs as a light-amber to faintly yellow-colored, vitreous, brittle solid. It is practically odorless and tasteless and is available as translucent sheets and granules, or as a powder.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acidity/alkalinity: for a 1% w/v aqueous solution at 25°C:

pH = 3.8–6.0 (type A);
pH = 5.0–7.4 (type B).

Density:
1.325 g/cm^3 for type A;
1.283 g/cm^3 for type B.

Isoelectric point:
7–9 for type A;
4.7–5.3 for type B.

Moisture content: 9–11%.(9) *See also* Figures 1 and 2.

Table I: Pharmacopeial specifications for gelatin.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Microbial contamination	—	≤1000/g	+
Residue on ignition	≤2.0%	—	≤2.0%
Loss on drying	≤15.0%	≤15.0%	—
Odor and water-insoluble substances	—	—	+
Isoelectric point	+	+	+
Type A	7.0–9.0	6.0–9.5	—
Type B	4.5–5.0	4.7–5.6	—
Conductivity	—	≤1 mS/cm	—
Sulfur dioxide	—	≤50 ppm	≤0.15%
Sulfite	+	—	—
Arsenic	≤1 ppm	—	≤0.8 ppm
Iron	—	≤30 ppm	—
Chromium	—	≤10 ppm	—
Zinc	—	≤30 ppm	—
Heavy metals	≤50 ppm	≤50 ppm	≤50 ppm
pH	—	3.8–7.6	—
Mercury	≤0.1 ppm	—	—
Peroxides	—	≤10 ppm	—
Phenolic preservatives	—	+	—
Gel strength	—	+	—

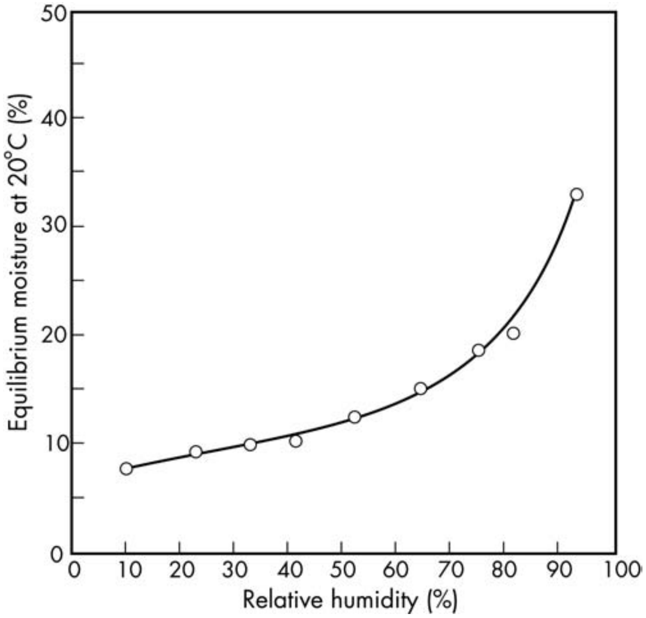

Figure 1: Equilibrium moisture content of gelatin (*Pharmagel A*).

Solubility: practically insoluble in acetone, chloroform, ethanol (95%), ether, and methanol. Soluble in glycerin, acids, and alkalis, although strong acids or alkalis cause precipitation. In water, gelatin swells and softens, gradually absorbing between five and 10 times its own weight of water. Gelatin is soluble in hot water, forming a jelly, or gel, on cooling to 35–40°C. At temperatures >40°C, the system exists as a sol. This gel–sol system is heat-reversible, the melting temperature being slightly higher than the setting point; the melting point can be varied by the addition of glycerin.

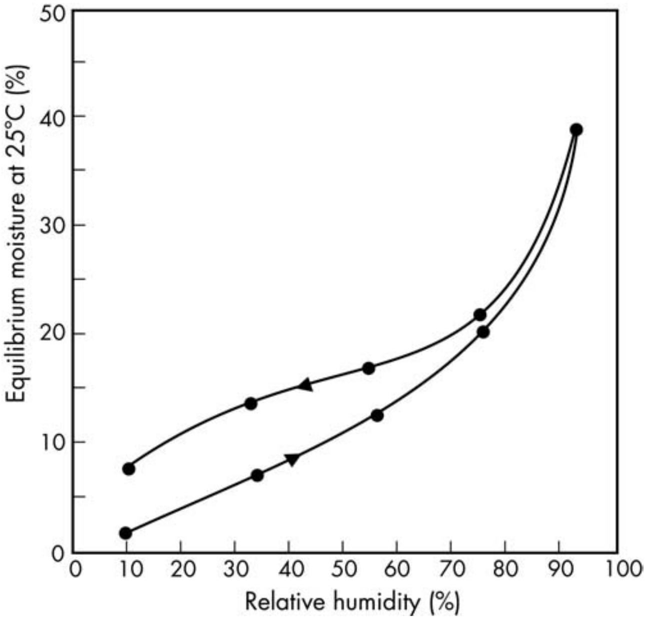

Figure 2: Sorption–desorption isotherm of gelatin.

Viscosity (dynamic):
4.3–4.7 mPa s (4.3–4.7 cP) for a 6.67% w/v aqueous solution at 60°C;
18.5–20.5 mPa s (18.5–20.5 cP) for a 12.5% w/v aqueous solution at 60°C.

11 Stability and Storage Conditions

Dry gelatin is stable in air. Aqueous gelatin solutions are also stable for long periods if stored under cool, sterile conditions. At temperatures above about 50°C, aqueous gelatin solutions may undergo slow depolymerization and a reduction in gel strength may occur on resetting. Depolymerization becomes more rapid at temperatures above 65°C, and gel strength may be reduced by half when a solution is heated at 80°C for 1 hour. The rate and extent of depolymerization depends on the molecular weight of the gelatin, with a lower-molecular-weight material decomposing more rapidly.(10)

Gelatin may be sterilized by dry heat.

The bulk material should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Gelatin is an amphoteric material and will react with both acids and bases. It is also a protein and thus exhibits chemical properties characteristic of such materials; for example, gelatin may be hydrolyzed by most proteolytic systems to yield its amino acid components.

Gelatin will also react with aldehydes and aldehydic sugars, anionic and cationic polymers, electrolytes, metal ions, plasticizers, preservatives, and surfactants. It is precipitated by alcohols, chloroform, ether, mercury salts, and tannic acid. Gels can be liquefied by bacteria unless preserved.

Some of these interactions are exploited to favorably alter the physical properties of gelatin; for example, gelatin is mixed with a plasticizer, such as glycerin, to produce soft gelatin capsules and suppositories; *see* Section 7.

13 Method of Manufacture

Gelatin is extracted from animal tissues rich in collagen such as skin, sinews, and bone. Although it is possible to extract gelatin from these materials using boiling water, it is more practical to first pretreat the animal tissues with either acid or alkali. Gelatin obtained from the acid process is called type A, whereas gelatin obtained from the alkali process is called type B.

In the USA, most type A gelatin is obtained from pig skins. This material is washed in cold water for a few hours to remove extraneous matter and is then digested in dilute mineral acid (HCl, H_2SO_4, H_2SO_3, or H_3PO_4) at pH 1–3 and 15–20°C until maximum swelling has occurred. This process takes approximately 24 hours. The swollen stock is then washed with water to remove excess acid, and the pH is adjusted to pH 3.5–4.0 for the conversion to gelatin by hot-water extraction.

The hydrolytic extraction is carried out in a batch-type operation using successive portions of hot water at progressively higher temperatures until the maximum yield of gelatin is obtained. The gelatin solution is then chilled to form jelled sheets, which are dried in temperature-controlled ovens. The dried gelatin is ground to the desired particle size.

In the alkali process, demineralized bones (ossein) or cattle skins are usually used. The animal tissue is held in a calcium hydroxide (lime) slurry for a period of 1–3 months at 15–20°C. At the end of the liming, the stock is washed with cold water to remove as much of the lime as possible. The stock solution is then neutralized with acid (HCl, H_2SO_4, H_3PO_4) and the gelatin is extracted with water in an identical manner to that in the acid process.

During the preparation of the bovine bones used in the production of gelatin, specified risk materials that could contain Transmissible Spongiform Encephalopathies (TSEs) vectors are removed. TSE infectivity is not present in pharmaceutical grade gelatin.

14 Safety

Gelatin is widely used in a variety of pharmaceutical formulations including oral and parenteral products.

In general, when used in oral formulations gelatin may be regarded as a nontoxic and nonirritant material. However, there have been rare reports of gelatin capsules adhering to the esophageal lining, which may cause local irritation.(11) Hypersensitivity reactions, including serious anaphylactoid reactions, have been reported following the use of gelatin in parenteral products.(8)

There have been concerns over the potential spread of BSE/TSE infections through bovine derived products. However, the risk of such contamination of medicines is extremely low, to the point of being theoretical.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Gelatin should be handled in a well-ventilated environment.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (dental preparations; inhalations; injections; oral capsules, pastilles, solutions, syrups and tablets; topical and vaginal preparations). Included in medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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18 Comments

In the past there has been a significant amount of regulatory activity due to the attention given to bovine sourced gelatin manufacturing processes and the potential transmission of TSE vectors from raw bovine materials into gelatin. In Europe the criteria by which the safety is assured involves controlling the geographical sourcing of animals used; the nature of the tissue used (based on scientific data showing where animal BSE infectivity is located); and the method of production.

Gelatin produced with hides as the starting material is considered much safer than using bones, although it is recommended that measures are undertaken to prevent cross-contamination with potentially contaminated materials. When gelatin is produced from bones, the bones should ideally be produced from countries classified as Geographical BSE Risk (GBR) I and II, although bones from GBR III countries can be used if the removal of vertebrae from the raw materials is assured (*see* Table II).(12)

Various grades of gelatin are commercially available that differ in particle size, molecular weight, and other properties. Grading is usually by gel strength, expressed as 'Bloom strength', which is the weight in grams that, when applied under controlled conditions to a plunger 12.7 mm in diameter, will produce a depression exactly 4 mm deep in a matured gel containing 6.66% w/w of gelatin in water.

Gelatin–acacia complex coacervation has been used in the preparation of microcapsules of vitamin A.(13) Pindolol-loaded alginate–gelatin beads have been developed for the sustained release of pindolol.(14)

A specification for gelatin is contained in the Food Chemicals Codex (FCC).

The EINECS number for gelatin is 232-554-6.

Table II: The European Scientific Steering Committee classification of geographical BSE risk (GBR).

GBR level	Presence of one or more cattle clinically or pre-clinically infected with BSE in a geographical region/country
I	Highly unlikely
II	Unlikely but not excluded
III	Likely but not confirmed or confirmed at a lower level
IV	Confirmed at a higher level

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JC Price.

22 Date of Revision

23 August 2005.

Glucose, Liquid

1 Nonproprietary Names

BP: Liquid glucose
PhEur: Glucosum liquidum
USPNF: Liquid glucose

2 Synonyms

Corn syrup; *C*PharmSweet*; *Flolys*; *Glucomalt*; glucose syrup; *Glucosweet*; *Mylose*; *Roclys*; starch syrup.

3 Chemical Name and CAS Registry Number

Liquid glucose.

4 Empirical Formula and Molecular Weight

See Section 8.

5 Structural Formula

See Section 8.

6 Functional Category

Coating agent; sweetening agent; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Liquid glucose is used as a base in oral solutions and syrups and also as a granulating and coating agent in tablet manufacture. In sugar solutions for tablet coating, liquid glucose is used to retard the crystallization of the sucrose. Liquid glucose is also used in confectionery products. *See* Table I.

Table I: Uses of liquid glucose.

Use	Concentration (%)
Confectionery	20–60
Granulating agent	5–10
Oral syrup vehicle	20–60
Tablet coating	10–20

8 Description

Liquid glucose is an aqueous solution of several compounds, principally dextrose, dextrin, fructose, and maltose, with other oligosaccharides and polysaccharides. It is a colorless, odorless, and viscous sweet-tasting liquid, ranging in color from colorless to straw-colored.

Liquid glucose is classified into four categories according to its degree of hydrolysis, expressed as dextrose equivalent (DE):
Type I: 20–38 DE;
Type II: 38–58 DE;
Type III: 58–73 DE;
Type IV: >73 DE.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for liquid glucose.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Acidity	—	+
pH	4.0–6.0	—
Water	⩽30.0%	⩽21.0%
Residue on ignition	⩽0.5 %	⩽0.5%
Sulfur dioxide	⩽20 ppm(a)	—
Dextrose equivalent	⩽20.0%	—
Sulfite	—	+
Heavy metals	⩽10 ppm	⩽0.001%
Starch	—	+
Organic volatile impurities	—	+
Assay (of dried matter)	⩾70.0%	—

(a) Or ⩽400 ppm if intended for the production of hard boiled candies, provided the final product contains ⩽50 ppm.

10 Typical Properties

Density: 1.43 g/cm^3 at 20°C
Solubility: miscible with water; partially miscible with ethanol (90%).
Viscosity (dynamic): 13.0–14.5 mPa s (13.0–14.5 cP) at 21°C.

11 Stability and Storage Conditions

Liquid glucose should be stored in a well-closed container in a cool, dry place. Elevated temperatures will cause discoloration.

12 Incompatibilities

Incompatible with strong oxidizing agents.

13 Method of Manufacture

Liquid glucose is prepared by the incomplete acidic or enzymatic hydrolysis of starch.

14 Safety

Liquid glucose is used in oral pharmaceutical formulations and confectionery products and is generally regarded as a nontoxic and nonirritant material. It may be consumed by diabetics.

See also Dextrose.

LD_{50} (mouse, IV): 9 g/kg(1)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral solutions, syrups, and tablets; topical emulsions and gels). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Dextrin; dextrose; maltose.

18 Comments

A specification for glucose syrup is contained in the Food Chemicals Codex (FCC). The PhEur 2005 also includes a specification for glucose, liquid, spraydried

The EINECS number for glucose is 200-075-1.

19 Specific References

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A Day.

22 Date of Revision

1 August 2005.

Glycerin

1 Nonproprietary Names

BP: Glycerol
JP: Concentrated glycerin
PhEur: Glycerolum
USP: Glycerin

2 Synonyms

Croderol; E422; glycerine; *Glycon G-100*; *Kemstrene*; *Optim*; *Pricerine*; 1,2,3-propanetriol; trihydroxypropane glycerol.

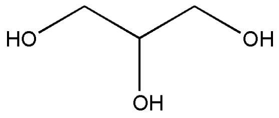
3 Chemical Name and CAS Registry Number

Propane-1,2,3-triol [56-81-5]

4 Empirical Formula and Molecular Weight

$C_3H_8O_3$ 92.09

5 Structural Formula



6 Functional Category

Antimicrobial preservative; emollient; humectant; plasticizer; solvent; sweetening agent; tonicity agent.

7 Applications in Pharmaceutical Formulation or Technology

Glycerin is used in a wide variety of pharmaceutical formulations including oral, otic, ophthalmic, topical, and parenteral preparations; *see* Table I.

In topical pharmaceutical formulations and cosmetics, glycerin is used primarily for its humectant and emollient properties. In parenteral formulations, glycerin is used mainly as a solvent.(1)

In oral solutions, glycerin is used as a solvent, sweetening agent, antimicrobial preservative, and viscosity-increasing agent. It is also used as a plasticizer and in film coatings.(2,3) Glycerin is additionally used in topical formulations such as creams and emulsions.(4)

Glycerin is used as a plasticizer of gelatin in the production of soft-gelatin capsules and gelatin suppositories.

Glycerin is employed as a therapeutic agent in a variety of clinical applications,(5) and is also used as a food additive.

Table I: Uses of glycerin.

Use	Concentration (%)
Antimicrobial preservative	<20
Emollient	≤30
Humectant	≤30
Ophthalmic formulations	0.5–3.0
Plasticizer in tablet film coating	Variable
Solvent for parenteral formulations	≤50
Sweetening agent in alcoholic elixirs	≤20

8 Description

Glycerin is a clear, colorless, odorless, viscous, hygroscopic liquid; it has a sweet taste, approximately 0.6 times as sweet as sucrose.

9 Pharmacopeial Specifications

See Table II. *See also* Section 18.

Table II: Pharmacopeial specifications for glycerin.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	+	+	—
Appearance of solution	+	+	+
Acidity or alkalinity	+	+	—
Refractive index	≤1.470	1.470–1.475	—
Aldehydes	—	≤10 ppm	—
Related substances	—	+	—
Halogenated compounds	—	≤35 ppm	—
Limit of chlorinated compounds	—	—	+
Sugars	—	+	—
Chloride	≤0.001%	≤10 ppm	≤0.001%
Heavy metals	≤5 ppm	≤5 ppm	≤5 μg/g
Water	—	≤2.0%	≤5.0%
Sulfated ash	≤0.01%	≤0.01%	≤0.01%
Specific gravity	≥1.258	—	≥1.249
Sulfate	≤0.002%	—	≤0.002%
Esters	—	+	—
Ammonium	+	—	—
Calcium	+	—	—
Arsenic	≤2 ppm	—	—
Acrolein, glucose or other reducing substances	+	—	—
Fatty acids and esters	+	+	+
Organic volatile impurities	—	—	+
Readily carbonizable substances	+	—	—
Assay	≥98.0%	98.0–101.0%	99.0–101.0%

10 Typical Properties

Boiling point: 290°C (with decomposition)
Density:
1.2656 g/cm^3 at 15°C;
1.2636 g/cm^3 at 20°C;
1.2620 g/cm^3 at 25°C.
Flash point: 176°C (open cup)
Freezing point: *see* Table III.
Hygroscopicity: hygroscopic.
Melting point: 17.8°C
Osmolarity: a 2.6% v/v aqueous solution is isoosmotic with serum.
Refractive index:
n_D^{15} = 1.4758;
n_D^{20} = 1.4746;
n_D^{25} = 1.4730.
Solubility: *see* Table IV.
Specific gravity: *see* Table V.
Surface tension: 63.4 mN/m (63.4 dynes/cm) at 20°C.
Vapor density (relative): 3.17 (air = 1)
Viscosity (dynamic): *see* Table VI.

Table III: Freezing points of aqueous glycerin solutions.

Concentration of aqueous glycerin solution (% w/w)	Freezing point (°C)
10.0	−1.6
20.0	−4.8
30.0	−9.5
40.0	−15.4
50.0	−23
60.0	−34.7
66.7	−46.5
80.0	−20.3
90.0	−1.6

Table IV: Solubility of glycerin.

Solvent	Solubility at 20°C
Acetone	Slightly soluble
Benzene	Practically insoluble
Chloroform	Practically insoluble
Ethanol (95%)	Soluble
Ether	1 in 500
Ethyl acetate	1 in 11
Methanol	Soluble
Oils	Practically insoluble
Water	Soluble

Table V: Specific gravity of glycerin.

Concentration of aqueous glycerin solution (% w/w)	Specific gravity at 20°C
10	1.024
20	1.049
30	1.075
40	1.101
50	1.128
60	1.156

Table VI: Viscosity (dynamic) of aqueous glycerin solutions.

Concentration of aqueous glycerin solution (% w/w)	Viscosity at 20°C (mPa s)
5	1.143
10	1.311
25	2.095
50	6.05
60	10.96
70	22.94
83	111.0

11 Stability and Storage Conditions

Glycerin is hygroscopic. Pure glycerin is not prone to oxidation by the atmosphere under ordinary storage conditions but it decomposes on heating, with the evolution of toxic acrolein. Mixtures of glycerin with water, ethanol (95%), and propylene glycol are chemically stable.

Glycerin may crystallize if stored at low temperatures; the crystals do not melt until warmed to 20°C.

Glycerin should be stored in an airtight container, in a cool, dry place.

12 Incompatibilities

Glycerin may explode if mixed with strong oxidizing agents such as chromium trioxide, potassium chlorate, or potassium permanganate. In dilute solution, the reaction proceeds at a slower rate with several oxidation products being formed. Black discoloration of glycerin occurs in the presence of light, or on contact with zinc oxide or basic bismuth nitrate.

An iron contaminant in glycerin is responsible for the darkening in color of mixtures containing phenols, salicylates, and tannin.

Glycerin forms a boric acid complex, glyceroboric acid, that is a stronger acid than boric acid.

13 Method of Manufacture

Glycerin is mainly obtained from oils and fats as a by-product in the manufacture of soaps and fatty acids. It may also be obtained from natural sources by fermentation of, for example, sugar beet molasses in the presence of large quantities of sodium sulfite. Synthetically, glycerin may be prepared by the chlorination and saponification of propylene.

14 Safety

Glycerin occurs naturally in animal and vegetable fats and oils that are consumed as part of a normal diet. Glycerin is readily absorbed from the intestine and is either metabolized to carbon dioxide and glycogen or used in the synthesis of body fats.

Glycerin is used in a wide variety of pharmaceutical formulations including oral, ophthalmic, parenteral, and topical preparations. Adverse effects are mainly due to the dehydrating properties of glycerin.(5)

Oral doses are demulcent and mildly laxative in action. Large doses may produce headache, thirst, nausea, and hyperglycemia. The therapeutic parenteral administration of very large glycerin doses, 70–80 g over 30–60 minutes in adults to reduce cranial pressure, may induce hemolysis, hemoglobinuria, and renal failure.(6) Slower administration has no deleterious effects.(7)

Glycerin may also be used orally in doses of 1.0–1.5 g/kg body-weight to reduce intraocular pressure.

When used as an excipient or food additive, glycerin is not usually associated with any adverse effects and is generally regarded as a nontoxic and nonirritant material.

LD_{50} (guinea pig, oral): 7.75 g/kg(8)
LD_{50} (mouse, IP): 8.98 g/kg
LD_{50} (mouse, IV): 4.25 g/kg
LD_{50} (mouse, oral): 4.1 g/kg
LD_{50} (mouse, SC): 0.09 g/kg
LD_{50} (rabbit, IV): 0.05 g/kg
LD_{50} (rat, IP): 4.42 g/kg
LD_{50} (rat, oral): 12.6 g/kg
LD_{50} (rat, SC): 0.1 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. In the UK, the recommended long-term (8-hour TWA) exposure limit for glycerin mist is 10 mg/m^3.(9) Glycerin is combustible and may react explosively with strong oxidizing agents; *see* Section 12.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (dental pastes; buccal preparations; inhalations; injections; nasal and ophthalmic preparations; oral capsules, solutions, suspensions and tablets; otic, rectal, topical, transdermal, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

—

18 Comments

The EINECS number for glycerin is 200-289-5.

Some pharmacopeias also contain specifications for diluted glycerin solutions. The JP 2001 contains a monograph for 'glycerin' that contains 84–87% of propane-1,2,3-triol ($C_3H_8O_3$). The PhEur 2005 contains a monograph for 'glycerol 85 per cent' that contains 83.5–88.5% of propane-1,2,3-triol ($C_3H_8O_3$). A specification for glycerin is contained in the Food Chemicals Codex (FCC).

19 Specific References

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21 Authors

JC Price.

22 Date of Revision

24 August 2005.

Glyceryl Behenate

1 Nonproprietary Names

BP: Glycerol dibehenate
PhEur: Glyceroli dibehenas
USPNF: Glyceryl behenate

2 Synonyms

Compritol 888 ATO; 2,3-dihydroxypropyl docosanoate; docosanoic acid, 2,3-dihydroxypropyl ester; E471; glycerol behenate; glyceryl monobehenate.

Note that tribehenin is used as a synonym for glyceryl tribehenate.

3 Chemical Name and CAS Registry Number

Docosanoic acid, monoester with glycerin [30233-64-8] (glyceryl behenate)
Docosanoic acid, diester with glycerin [94201-62-4] (glyceryl dibehenate)
Docosanoic acid, triester with glycerin [18641-57-1] (glyceryl tribehenate)

4 Empirical Formula and Molecular Weight

The PhEur 2005 (Suppl. 5.1) describes glyceryl dibehenate as a mixture of diacylglycerols, mainly dibehenoylglycerol, together with variable quantities of mono- and triacylglycerols (*see* Section 9). The USPNF 23 describes glyceryl behenate as a mixture of glycerides of fatty acids, mainly behenic acid. It specifies that the content of 1-monoglycerides should be 12.0–18.0%.

5 Structural Formula

See Section 4.

6 Functional Category

Coating agent; tablet binder; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Glyceryl behenate is used in cosmetics, foods, and oral pharmaceutical formulations. In cosmetics, it is mainly used as a viscosity-increasing agent in emulsions; *see* Table I.

In pharmaceutical formulations, glyceryl behenate is mainly used as a tablet and capsule lubricant(1–3) and as a lipidic coating excipient. It has been investigated for the encapsulation of various drugs such as retinoids.(4) It has also been investigated for use in the preparation of sustained release tablets; (5–10) as a matrix-forming agent for the controlled release of water-soluble drugs;(10) and as a lubricant in oral solid dosage formulations, and it can also be used as a hot-melt coating agent sprayed onto a powder.(11)

Table I: Uses of glyceryl behenate.

Use	Concentration (%)
Lipophilic matrix or coating for sustained-released tablets and capsules	>10.0
Tablet and capsule lubricant	1.0–3.0
Viscosity-increasing agent in silicon gels (cosmetics)	1.0–15.0
Viscosity-increasing agent in w/o or o/w emulsions (cosmetics)	1.0–5.0

8 Description

Glyceryl behenate occurs as a fine white powder or hard waxy mass with a faint odor.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for glyceryl behenate.

Test	PhEur 2005 (Suppl. 5.1)	USPNF 23
Identification	+	+
Characters	+	—
Acid value	$\leqslant 4.0$	$\leqslant 4$
Iodine value	$\leqslant 3.0$	$\leqslant 3$
Saponification value	145–165	145–165
Residue on ignition	$\leqslant 0.1\%$	$\leqslant 0.1\%$
Nickel	$\leqslant 1$ ppm	—
Water	$\leqslant 1.0\%$	—
Heavy metals	—	$\leqslant 0.001\%$
Melting point	65–77°C	—
Content of 1-monoglycerides	—	12.0–18.0%
Content of acylglycerols (glycerides)	+	—
Monoacylglycerols	15.0–20.0%	—
Diacylglycerols	40–60%	—
Triacylglycerols	21–35%	—
Free glycerin	$\leqslant 1.0\%$	$\leqslant 1.0\%$
Organic volatile impurities	—	+
Composition of fatty acids	+	—
Arachidic acid	$\leqslant 10.0\%$	—
Behenic acid	$\geqslant 83.0\%$	—
Erucic acid	$\leqslant 3.0\%$	—
Lignoceric acid	$\leqslant 3.0\%$	—
Palmitic acid	$\leqslant 3.0\%$	—
Stearic acid	$\leqslant 5.0\%$	—

10 Typical Properties

Melting point: 65–77°C
Solubility: soluble, when heated, in chloroform and dichloromethane, practically insoluble in ethanol (95%), hexane, mineral oil, and water.

11 Stability and Storage Conditions

Glyceryl behenate should be stored in a tight container, at a temperature less than 35°C.

12 Incompatibilities

—

13 Method of Manufacture

Glyceryl behenate is prepared by the esterification of glycerin by behenic acid (C_{22} fatty acid) without the use of catalysts. In the case of *Compritol 888 ATO* (Gattefossé), raw materials used are of vegetable origin, and the esterified material is atomized by spray-cooling.

14 Safety

Glyceryl behenate is used in cosmetics, foods and oral pharmaceutical formulations and is generally regarded as a relatively nonirritant and nontoxic material.

LD_{50} (mouse, oral): 5 g/kg(12)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantities of material handled. Glyceryl behenate emits acrid smoke and irritating fumes when heated to decomposition.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (capsules and tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Glyceryl palmitostearate.

18 Comments

The EINECS numbers are: 250-097-0 for glyceryl behenate; 303-650-6 for glyceryl dibehenate; 242-471-7 for glyceryl tribehenate.

19 Specific References

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21 Authors

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22 Date of Revision

12 August 2005.

Glyceryl Monooleate

1 Nonproprietary Names

BP: Glycerol mono-oleates
PhEur: Glyceroli mono-oleates
USPNF: Glyceryl monooleate

2 Synonyms

Aldo MO; *Atlas G-695*; *Capmul GMO*; glycerol-1-oleate; glyceryl mono-oleate; *Kessco GMO*; *Ligalub*; monolein; *Monomuls 90-O18*; mono-olein; α-mono-olein glycerol; *Peceol*; *Priolube 1408*; *Stepan GMO*; *Tegin*.

3 Chemical Name and CAS Registry Number

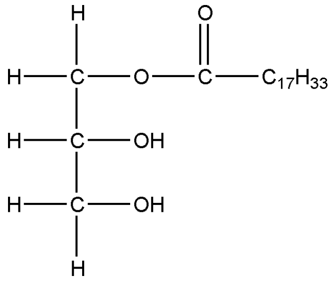
9-Octadecenoic acid (Z), monoester with 1,2,3-propanetriol [25496-72-4]

4 Empirical Formula and Molecular Weight

$C_{21}H_{40}O_4$ 356.55 (for pure material)

Glyceryl monooleate is a mixture of the glycerides of oleic acid and other fatty acids, consisting mainly of the monooleate; *see* Section 8.

5 Structural Formula



6 Functional Category

Bioadhesive; emollient; emulsifying agent; emulsion stabilizer; gelling agent; mucoadhesive; nonionic surfactant; sustained-release agent.

7 Applications in Pharmaceutical Formulation or Technology

Glyceryl monooleate is a polar lipid that swells in water to give several phases with different rheological properties.(1) It is available in both nonemulsifying (n/e) and self-emulsifying (s/e) grades, the self-emulsifying grade containing about 5% of an anionic surfactant.

The nonemulsifying grade is used in topical formulations as an emollient and as an emulsifying agent for water-in-oil emulsions. It is also a stabilizer for oil-in-water emulsions. The self-emulsifying grade is used as a primary emulsifier for oil-in-water systems.(2)

Glyceryl monooleate gels in excess water, forming a highly ordered cubic phase that can be used to sustain the release of various water-soluble drugs.(3–6) It is also the basis of mucoadhesive drug delivery systems.(7,8)

Glyceryl monooleate is reported to enhance transdermal(9) and buccal penetration.(10)

8 Description

The PhEur 2005 (Suppl. 5.1) describes glyceryl monooleate as being a mixture of monoacylglycerols, mainly mono-oleoylglycerol, together with variable quantities of di- and triacylglycerols. They are defined by the nominal content of monoacylglycerols (*see* Table I) and obtained by partial glycerolysis of vegetable oils mainly containing triacylglycerols of oleic acid or by esterification of glycerol by oleic acid, this fatty acid being of vegetable or animal origin. A suitable antioxidant may be added.

Glyceryl monooleates occur as amber oily liquids, which may be partially solidified at room temperature and have a characteristic odor.

Table I: Nominal content of acylglycerols in glycerol monooleate defined in the PhEur 2005 (Suppl. 5.1).

	Nominal content of acylglycerol (%)		
	40	**60**	**90**
Monoacylglycerols	32.0–52.0	55.0–65.0	90.0–101.0
Diacylglycerols	30.0–50.0	15.0–35.0	<10.0
Triacylglycerols	5.0–20.0	2.0–10.0	<2.0

9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Boiling point: 238–240°C
Density: 0.942 g/cm^3
Flash point: 216°C
HLB value: 3.3 (n/e); 4.1 (s/e).
Melting point: 35°C (*see also* Section 13)
Refractive index: 1.4626
Solubility: soluble in chloroform, ethanol (95%), ether, mineral oil, and vegetable oils; practically insoluble in water. The self-emulsifying grade is dispersible in water.
Viscosity (kinematic): 100 m^2/s (100 cSt) at 40°C

11 Stability and Storage Conditions

Glyceryl monooleate should be stored in an airtight container, protected from light in a cool, dry place.

Table II: Pharmacopeial specifications for glyceryl monooleate.

Test	PhEur 2005 (Suppl. 5.1)	USPNF 23
Identification	+	+
Characters	+	+
Acid value	⩽6.0%	⩽6.0%
Iodine value	65.0–95.0	65.0–95.0
Peroxide value	⩽12.0%	⩽12.0%
Saponification value	150–170	150–170
Free glycerol	⩽6.0%	⩽6.0%
Composition of fatty acids		
Palmitic acid	⩽12.0%	⩽12.0%
Stearic acid	⩽6.0%	⩽6.0%
Oleic acid	⩾60.0%	⩾60.0%
Linoleic acid	⩽35.0%	⩽35.0%
Linolenic acid	⩽2.0%	⩽2.0%
Arachidic acid	⩽2.0%	⩽2.0%
Eicosenoic acid	⩽2.0%	⩽2.0%
Content of acylglycerol	*see* Table I	—
Water	⩽1.0%	⩽1.0%
Total ash	⩽0.1%	⩽0.1%

12 Incompatibilities

Glyceryl monooleate is incompatible with strong oxidizing agents. The self-emulsifying grade is incompatible with cationic surfactants.

13 Method of Manufacture

Glyceryl monooleate is prepared by the esterification of glycerol with fatty acids, chiefly oleic acid. As the fatty acids are not pure substances, but rather a mixture of fatty acids, the product obtained from the esterification will contain a mixture of esters, including stearic and palmitic. Di- and tri-esters may also be present. The composition and, therefore, the physical properties of glyceryl monooleate may thus vary considerably from manufacturer to manufacturer; e.g., the melting point may vary from 10–35°C.

14 Safety

Glyceryl monooleate is used in oral and topical pharmaceutical formulations and is generally regarded as a relatively nonirritant and nontoxic excipient.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral capsules, oral powder, oral tablets; creams, controlled-release transdermal films). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Glyceryl monostearate.

18 Comments

A specification for glyceryl monooleate is included in the Food Chemicals Codex (FCC).

The EINECS number for glyceryl monooleate is 247-038-6.

19 Specific References

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21 Authors

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22 Date of Revision

15 August 2005.

Glyceryl Monostearate

1 Nonproprietary Names

BP: Glyceryl monostearate 40–55
JP: Glyceryl monostearate
PhEur: Glyceroli monostearas 40–55
USPNF: Glyceryl monostearate
Note that the USPNF 23 also includes a specification for mono- and di-glycerides that corresponds to glyceryl monostearate 40–55 in the PhEur 2005.

2 Synonyms

Capmul GMS-50; *Cutina GMS*; 2,3-dihydroxypropyl octadecanoate; glycerine monostearate; glycerin monostearate; glycerol monostearate; glycerol stearate; glyceryl stearate; GMS; *Imwitor 191*; *Imwitor 900*; *Kessco GMS*; *Lipo GMS 410*; *Lipo GMS 450*; *Lipo GMS 600*; monoester with 1,2,3-propanetriol; monostearin; *Myvaplex 600P*; *Myvatex*; 1,2,3-propanetriol octadecanoate; *Protachem GMS-450*; *Rita GMS*; stearic acid, monoester with glycerol; stearic monoglyceride; *Stepan GMS*; *Tegin*; *Tegin 503*; *Tegin 515*; *Tegin 4100*; *Tegin M*; *Unimate GMS*.

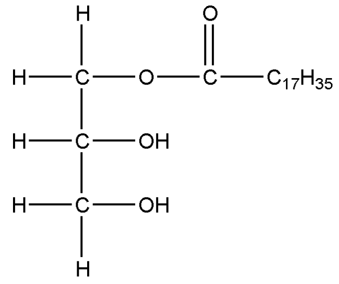
3 Chemical Name and CAS Registry Number

Octadecanoic acid, monoester with 1,2,3-propanetriol [31566-31-1]

4 Empirical Formula and Molecular Weight

$C_{21}H_{42}O_4$ 358.6

5 Structural Formula



6 Functional Category

Emollient; emulsifying agent; solubilizing agent; stabilizing agent; sustained-release ingredient; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

The many varieties of glyceryl monostearate are used as nonionic emulsifiers, stabilizers, emollients, and plasticizers in a variety of food, pharmaceutical, and cosmetic applications. It acts as an effective stabilizer, that is, as a mutual solvent for polar and nonpolar compounds that may form water-in-oil or oil-in-water emulsions.(1,2) These properties also make it useful as a dispersing agent for pigments in oils or solids in fats, or as a solvent for phospholipids, such as lecithin.

Glyceryl monostearate has also been used in a novel fluidized hot-melt granulation technique for the production of granules and tablets.(3)

Glyceryl monostearate is a lubricant for tablet manufacturing and may be used to form sustained-release matrices for solid dosage forms.(4–6) Sustained-release applications include the formulation of pellets for tablets(7) or suppositories(8) and the preparation of a veterinary bolus.(9) Glyceryl monostearate has also been used as a matrix ingredient for a biodegradable, implantable, controlled-release dosage form.(10)

When using glyceryl monostearate in a formulation, the possibility of polymorph formation should be considered. The α-form is dispersible and foamy, useful as an emulsifying agent or preservative. The denser, more stable, β-form is suitable for wax matrices. This application has been used to mask the flavor of clarithromycin in a pediatric formulation.(11)

8 Description

While the names glyceryl monostearate and mono- and di-glycerides are used for a variety of esters of long-chain fatty acids, the esters fall into two distinct grades:

40–55 percent monoglycerides: the PhEur 2005 describes glyceryl monostearate 40–55 as a mixture of monoacylglycerols, mostly monostearoylglycerol, together with quantities of di- and triacylglycerols. It contains 40–55% of monoacylglycerols, 30–45% of diacylglycerols, and 5–15% of triacylglycerols. This PhEur grade corresponds to mono- and di-glycerides USPNF, which has similar specifications (not less than 40% monoglycerides).

90 percent monoglycerides: the USPNF 23 (Suppl. 1) describes glyceryl monostearate as consisting of not less than 90% of monoglycerides, chiefly glyceryl monostearate ($C_{21}H_{42}O_4$) and glyceryl monopalmitate ($C_{19}H_{38}O_4$).

The commercial products are mixtures of variable proportions of glyceryl monostearate and glyceryl monopalmitate.

Glyceryl monostearate is a white to cream-colored, waxlike solid in the form of beads, flakes, or powder. It is waxy to the touch and has a slight fatty odor and taste.

9 Pharmacopeial Specifications

Table I compares the specifications for the 40–55% grades. Glyceryl monostearate PhEur and mono- and di-glycerides USPNF. PhEur divides glyceryl monostearate 40–55 into three types according to the proportion of stearic acid ester in the mixture, and those specifications are presented in Table II. Table III presents the specifications for glyceryl monostearate USPNF (90% monoglycerides). Since the JP specifications are broad enough to encompass both grades, JP is included in both Table I and Table III.

Table I: Pharmacopeial specifications for glyceryl monostearate (40–55%).

Test	JP 2001	PhEur 2005	USPNF 23(a)
Identification	+	+	—
Acid value	≤15.0	≤3.0	≤4.0
Iodine value	≤3.0	≤3.0	≤3.0
Hydroxyl value	—	—	300–330
Saponification value	157–170	158–177	155–165
Melting point	≥55°C	—	—
Residue on ignition	≤0.10%	≤0.10%	≤0.1%
Acidity or alkalinity	+	—	—
Free glycerin	—	≤6.0%	≤7.0%
Composition of fatty acids	—	*see* Table II	—
Heavy metals	—	—	≤0.001%
Nickel	—	≤1 ppm	—
Water	—	≤1.0%	—
Organic volatile impurities	—	—	+
Assay (monoglycerides)	—	40.0–55.0%	≤40.0%(b)

(a) mono- and di-glycerides

(b) 90.0–110.0% of labeled amount

Table II: Specifications for the composition of fatty acids in glyceryl monostearate 40–55.

Glyceryl monostearate	Fatty acid used in manufacturing	Composition of fatty acids	
		Stearic acid	Sum of palmitic and stearic acids
Type I	Stearic acid 50	40.0–60.0%	≤90.0%
Type II	Stearic acid 70	60.0–80.0%	≤90.0%
Type III	Stearic acid 95	90.0–99.0%	≤96.0%

Table III: Pharmacopeial specifications for glyceryl monostearate (90%).

Test	JP 2001	USPNF 23
Identification	+	—
Acid value	≤15.0	≤6.0
Iodine value	≤3.0	≤3.0
Hydroxyl value	—	300–330
Saponification value	157–170	155–165
Melting point	≥55°C	≥55°C
Residue on ignition	≤0.10%	≤0.5%
Acidity or alkalinity	+	—
Limit of free glycerin	—	≤1.2%
Composition of fatty acids	—	—
Heavy metals	—	≤0.001%
Organic volatile impurities	—	+
Assay (monoglycerides)	—	≤90.0%

10 Typical Properties

A wide variety of glyceryl monostearate grades are commercially available, including self-emulsifying grades that contain small amounts of soap or other surfactants. Most grades are tailored for specific applications or made to user specifications and therefore have varied physical properties.

HLB value: 3.8

Flash point: ≈240°C

Melting point: 55–60°C

Polymorphs: The α-form is converted to the β-form when heated at 50°C.(12)

Solubility: soluble in hot ethanol, ether, chloroform, hot acetone, mineral oil, and fixed oils. Practically insoluble in water, but may be dispersed in water with the aid of a small amount of soap or other surfactant.

Specific gravity: 0.92

11 Stability and Storage Conditions

If stored at warm temperatures, glyceryl monostearate increases in acid value upon aging owing to the saponification of the ester with trace amounts of water. Effective antioxidants may be added, such as butylated hydroxytoluene and propyl gallate.

Glyceryl monostearate should be stored in a tightly closed container in a cool, dry place, and protected from light.

12 Incompatibilities

The self-emulsifying grades of glyceryl monostearate are incompatible with acidic substances.

13 Method of Manufacture

Glyceryl monostearate is prepared by the reaction of glycerin with triglycerides from animal or vegetable sources, producing a mixture of monoglycerides and diglycerides. The diglycerides may be further reacted to produce the 90% monoglyceride grade. Another process involves reaction of glycerol with stearoyl chloride.

The starting materials are not pure substances and therefore the products obtained from the processes contain a mixture of esters, including palmitate and oleate. Consequently, the composition, and therefore the physical properties, of glyceryl monostearate may vary considerably depending on the manufacturer.

14 Safety

Glyceryl monostearate is widely used in cosmetics, foods, and oral and topical pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material.

LD_{50} (mouse, IP): 0.2 g/kg(13)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets; ophthalmic, otic, rectal, topical, transdermal, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

If glyceryl monostearate is produced from animal fats (tallow), there may be additional regulatory requirements that the source be free of contamination from bovine spongiform encephalopathy.

17 Related Substances

Glyceryl monooleate; glyceryl palmitostearate; self-emulsifying glyceryl monostearate.

Self-emulsifying glyceryl monostearate

Comments: a specification for self-emulsifying glyceryl monostearate was previously included in the PhEur. Self-emulsifying glyceryl monostearate is a grade of glyceryl monostearate to which an emusifying agent has been added. The emulsifier may be a soluble soap, a salt of a sulfated alcohol, a nonionic surfactant, or a quaternary compound. It is used primarily as an emulsifying agent for oils, fats, solvents, and waxes. Aqueous preparations should contain an antimicrobial preservative.

18 Comments

Glyceryl monostearate and other fatty acid monoesters are not efficient emulsifiers. However, they are useful emollients that are readily emulsified by common emulsifying agents and by incorporation of other fatty materials into the formulation. Addition of the monoester materials provides the creams with smoothness, fine texture, and improved stability.

In topical applications, glyceryl monostearate is less drying than straight stearate creams, and is not drying when used in protective applications. A specification for glyceryl monostearate is contained in the Food Chemicals Codex (FCC).

19 Specific References

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AK Taylor.

22 Date of Revision

20 May 2005.

Glyceryl Palmitostearate

1 Nonproprietary Names

None adopted.

2 Synonyms

Glycerin palmitostearate; glycerol palmitostearate; 2-[(1-oxohexadecyl)-oxy]-1,3-propanediyl dioctadecanoate and 1,2,3-propane triol; *Precirol ATO 5*.

3 Chemical Name and CAS Registry Number

Octadecanoic acid, 2,3-dihydroxypropyl ester mixed with 3-hydroxy-2-[(1-oxohexadecyl)-oxy] propyl octadecanoate [8067-32-1]

4 Empirical Formula and Molecular Weight

Glyceryl palmitostearate is a mixture of mono-, di-, and triglycerides of C_{16} and C_{18} fatty acids.

5 Structural Formula

See Sections 3 and 4.

6 Functional Category

Biodegradable material; coating agent; gelling agent; release modifying agent; sustained-release agent; tablet and capsule diluent; tablet and capsule lubricant; taste-masking agent.

7 Applications in Pharmaceutical Formulation or Technology

Glyceryl palmitostearate is used in oral solid-dosage pharmaceutical formulations as a lubricant.(1,2) Disintegration times increase(3) and tablet strength decreases(4) with increase in mixing time.

It is used as a lipophilic matrix for sustained-release tablet and capsule formulations.(5,6) Tablet formulations may be prepared by either granulation or a hot-melt technique,(7,8) the former producing tablets that have the faster release profile. Release rate decreases with increased glyceryl palmitostearate content.(5)

Glyceryl palmitostearate is used to form microspheres, which may be used in capsules or compressed to form tablets,(9,10) pellets,(11) coated beads,(12) and biodegradable gels.(13) It is also used for taste-masking.(14) *See* Table I.

Table I: Uses of glyceryl palmitostearate.(14)

Use	Concentration (%)
Matrix for sustained release	10.0–25.0
Tablet masking	2.0–6.0
Tablet lubricant	1.0–3.0

8 Description

Glyceryl palmitostearate occurs as a fine white powder with a faint odor.

9 Pharmacopeial Specifications

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10 Typical Properties

Acid value: <6.0
Boiling point: 200°C
Color: <3 (Gardner scale)
Free glycerin content: <1.0%
Heavy metals: <10 ppm
Hydroxyl value: 60–115
Iodine value: <3
Melting point: 52–55°C
1-Monoglycerides content: 8.0–17.0%
Peroxide value: <3.0
Saponification value: 175–195
Solubility: freely soluble in chloroform and dichloromethane; practically insoluble in ethanol (95%), mineral oil, and water.
Sulfated ash: <0.1%
Unsaponifiable matter: <1.0%
Water content: <1.0%

11 Stability and Storage Conditions

Glyceryl palmitostearate should not be stored at temperatures above 35°C. For storage for periods over 1 month, glyceryl palmitostearate should be stored at a temperature of 5–15°C in an airtight container, protected from light and moisture.

12 Incompatibilities

Glyceryl palmitostearate is incompatible with ketoprofen(15) and naproxen.(16)

13 Method of Manufacture

Glyceryl palmitostearate is manufactured, without a catalyst, by the direct esterification of palmitic and stearic acids with glycerol.

14 Safety

Glyceryl palmitostearate is used in oral pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material.

LD_{50} (rat, oral): >6 g/kg(14)

15 Handling Precautions

Observe normal handling precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral suspension, oral tablet). Included in nonparenteral preparations licensed in Europe. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Glyceryl behenate; glyceryl monostearate.

18 Comments

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19 Specific References

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21 Authors

NA Armstrong.

22 Date of Revision

16 August 2005.

Glycofurol

1 Nonproprietary Names

None adopted.

2 Synonyms

Glycofurol 75; tetraglycol; α-(tetrahydrofuranyl)-ω-hydroxy-poly(oxyethylene); tetrahydrofurfuryl alcohol polyethylene glycol ether.

Note: tetraglycol is also used as a synonym for tetrahydrofurfuryl alcohol.

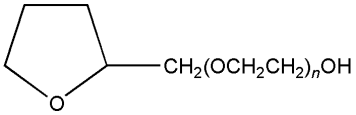
3 Chemical Name and CAS Registry Number

α-[(Tetrahydro-2-furanyl)methyl]-ω-hydroxy-poly(oxy-1,2-ethanediyl) [31692-85-0]

4 Empirical Formula and Molecular Weight

$C_9H_{18}O_4$ (average) 190.24 (average)

5 Structural Formula



Glycofurol 75: n = 1–2

6 Functional Category

Penetration enhancer; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Glycofurol is used as a solvent in parenteral products for intravenous or intramuscular injection in concentrations up to 50% v/v.(1–5) It has also been investigated, mainly in animal studies, for use as a penetration enhancer and solvent in topical(6) and intranasal formulations.(7–10) Glycofurol has also been used at 20% v/v concentration in a rectal formulation.(11)

8 Description

Glycofurol is a clear, colorless, almost odorless liquid, with a bitter taste; it produces a warm sensation on the tongue.

9 Pharmacopeial Specifications

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10 Typical Properties

Boiling point: 80–100°C for *Glycofurol 75*
Density: 1.070–1.090 g/cm^3 at 20°C
Hydroxyl value: 300–400
Moisture content: 0.2–5% at ambient temperature and 30% relative humidity.
Refractive index: n_D^{40} = 1.4545
Solubility: *see* Table I.

Table I: Solubility of glycofurol.

Solvent	Solubility at 20°C
Arachis oil	Immiscible
Castor oil	Miscible[a]
Ethanol (95%)	Miscible in all proportions
Glycerin	Miscible in all proportions
Isopropyl ether	Immiscible
Petroleum ether	Immiscible
Polyethylene glycol 400	Miscible in all proportions
Propan-2-ol	Miscible in all proportions
Propylene glycol	Miscible in all proportions
Water	Miscible in all proportions[a]

[a] Cloudiness may occur.

Viscosity (dynamic): 8–18 mPa s (8–18 cP) at 20°C for *Glycofurol 75*.

11 Stability and Storage Conditions

Stable if stored under nitrogen in a well-closed container protected from light, in a cool, dry place.

12 Incompatibilities

Incompatible with oxidizing agents.

13 Method of Manufacture

Glycofurol is prepared by the reaction of tetrahydrofurfuryl alcohol with ethylene oxide (followed by a special purification process in the case of *Glycofurol 75*).

14 Safety

Glycofurol is mainly used as a solvent in parenteral pharmaceutical formulations and is generally regarded as a relatively nontoxic and nonirritant material at the levels used as a pharmaceutical excipient. Glycofurol can be irritant when used undiluted; its tolerability is approximately the same as propylene glycol.(1,2)

Glycofurol may have an effect on liver function and may have a low potential for interaction with hepatoxins or those materials undergong extensive hepatic metabolism.(4)

LD_{50} (mouse, IV): 3.5 mL/kg(2)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Included in parenteral medicines licensed in Europe.

17 Related Substances

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18 Comments

Grades other than *Glycofurol 75* may contain significant amounts of tetrahydrofurfuryl alcohol and other impurities. *Glycofurol 75* meets an analytical specification which includes a requirement that the fraction in which $n = 1$ or 2 amounts to a minimum of 95%; *see* Section 5.

19 Specific References

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PJ Weller.

22 Date of Revision

14 August 2005.

Guar Gum

1 Nonproprietary Names

BP: Guar galactomannan
PhEur: Guar galactomannanum
USPNF: Guar gum

2 Synonyms

E412; *Galactosol*; guar flour; jaguar gum; *Meyprogat*; *Meyprodor*; *Meyprofin*.

3 Chemical Name and CAS Registry Number

Galactomannan polysaccharide [9000-30-0]

4 Empirical Formula and Molecular Weight

$(C_6H_{12}O_6)_n$ ≈220 000

See Section 5.

5 Structural Formula

Guar gum consists of linear chains of (1→4)-β-D-mannopyranosyl units with α-D-galactopyranosyl units attached by (1→6) linkages. The ratio of D-galactose to D-mannose is between 1 : 1.4 and 1 : 2. *See also* Section 8.

6 Functional Category

Suspending agent; tablet binder; tablet disintegrant; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Guar gum is a galactomannan, commonly used in cosmetics, food products, and pharmaceutical formulations. It has also been investigated in the preparation of sustained-release matrix tablets in the place of cellulose derivatives such as methylcellulose.(1)

In pharmaceuticals, guar gum is used in solid-dosage forms as a binder and disintegrant,(2–4) *see* Table I; in oral and topical products as a suspending, thickening, and stabilizing agent; and also as a controlled-release carrier. Guar gum has also been examined for use in colonic drug delivery.(5–9) Guar-gum-based three-layer matrix tablets have been used experimentally in oral controlled-release formulations.(10)

Therapeutically, guar gum has been used as part of the diet of patients with diabetes mellitus.(11,12) It has also been used as an appetite suppressant, although its use for this purpose, in tablet form, is now banned in the UK;(12–14) *see* Section 14.

Table I: Uses of guar gum.

Use	Concentration (%)
Emulsion stabilizer	1
Tablet binder	Up to 10
Thickener for lotions and creams	Up to 2.5

8 Description

The USPNF 23 describes guar gum as a gum obtained from the ground endosperms of *Cyamopsis tetragonolobus* (L.) Taub. (Fam. Leguminosae). It consists chiefly of a high-molecular-weight hydrocolloidal polysaccharide, composed of galactan and mannan units combined through glycoside linkages, which may be described chemically as a galactomannan. The PhEur 2005 similarly describes guar galactomannan as being obtained from the seeds of *Cyamopsis tetragonolobus* (L.) Taub. by grinding the endosperms and subsequent partial hydrolysis.

The main components are polysaccharides composed of D-galactose and D-mannose in molecular ratios of 1 : 1.4 to 1 : 2. The molecule consists of a linear chain of β-(1→4)-glycosidically linked manno-pyranoses and single α-(1→6)-glycosidically linked galacto-pyranoses. *See also* Section 18.

Guar gum occurs as an odorless or nearly odorless, white to yellowish-white powder with a bland taste.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for guar gum.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
pH (1% w/w solution)	5.5–7.5	—
Apparent viscosity	+	—
Microbial contamination	$\leqslant 10^3$/g	—
Loss on drying	⩽15.0%	⩽15.0%
Ash	⩽1.8%	⩽1.5%
Acid-insoluble matter	⩽7.0%	⩽7.0%
Arsenic	—	⩽3 ppm
Lead	—	⩽0.001%
Heavy metals	—	⩽0.002%
Protein	⩽5.0%	⩽10.0%
Starch	—	+
Galactomannans	—	⩾66.0%
Organic volatile impurities	—	+
Tragacanth, sterculia gum, agar, alginates, and carrageenan	+	—

10 Typical Properties

Acidity/alkalinity: pH = 5.0–7.0 (1% w/v aqueous dispersion)

Density: 1.492 g/cm^3

Solubility: practically insoluble in organic solvents. In cold or hot water, guar gum disperses and swells almost immediately to form a highly viscous, thixotropic sol. The optimum rate of hydration occurs at pH 7.5–9.0. Finely milled powders swell more rapidly and are more difficult to disperse. Two to four hours in water at room temperature are required to develop maximum viscosity.

Viscosity (dynamic): 4.86 Pa s (4860 cP) for a 1% w/v dispersion. Viscosity is dependent upon temperature, time, concentration, pH, rate of agitation, and particle size of the guar gum powder. Synergistic rheological effects may occur with other suspending agents such as xanthan gum; *see* Xanthan Gum.

11 Stability and Storage Conditions

Aqueous guar gum dispersions have a buffering action and are stable at pH 4.0–10.5. However, prolonged heating reduces the viscosity of dispersions.

The bacteriological stability of guar gum dispersions may be improved by the addition of a mixture of 0.15% methylparaben and 0.02% propylparaben as a preservative. In food applications, benzoic acid, citric acid, sodium benzoate, or sorbic acid may be used.

Guar gum powder should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Guar gum is compatible with most other plant hydrocolloids such as tragacanth. It is incompatible with acetone, ethanol (95%), tannins, strong acids, and alkalis. Borate ions, if present in the dispersing water, will prevent the hydration of guar gum. However, the addition of borate ions to hydrated guar gum produces cohesive structural gels and further hydration is then prevented. The gel formed can be liquefied by reducing the pH to below 7, or by heating.

Guar gum may reduce the absorption of penicillin V from some formulations by a quarter.(15)

13 Method of Manufacture

Guar gum is obtained from the ground endosperm of the guar plant, *Cyamopsis tetragonolobus* (L.) Taub. (Fam. Leguminosae), which is grown in India, Pakistan, and the semiarid southwestern region of the USA.

The seed hull can be removed by grinding, after soaking in sulfuric acid or water, or by charring. The embryo (germ) is removed by differential grinding, since each component possesses a different hardness. The separated endosperm, containing 80% galactomannan is then ground to different particle sizes depending upon final application.

14 Safety

Guar gum is widely used in foods and oral and topical pharmaceutical formulations. Excessive consumption may cause gastrointestinal disturbance such as flatulence, diarrhea, or nausea. Therapeutically, daily oral doses of up to 25 g of guar gum have been administered to patients with diabetes mellitus.(11)

Although it is generally regarded as a nontoxic and nonirritant material, the safety of guar gum when used as an appetite suppressant has been questioned. When consumed, the gum swells in the stomach to promote a feeling of fullness. However, it is claimed that premature swelling of guar gum tablets may occur and cause obstruction of, or damage to, the esophagus. Consequently, appetite suppressants containing guar gum in tablet form have been banned in the UK.(12) However, appetite suppressants containing microgranules of guar gum are claimed to be safe.(13) The use of guar gum for pharmaceutical purposes is unaffected by the ban.

In food applications, an acceptable daily intake of guar gum has not been specified by the WHO.(16)

LD_{50} (hamster, oral): 6.0 g/kg(17)
LD_{50} (mouse, oral): 8.1 g/kg
LD_{50} (rabbit, oral): 7.0 g/kg
LD_{50} (rat, oral): 6.77 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Guar gum may be irritating to the eyes. Eye protection, gloves, and a dust mask or respirator are recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral suspensions, syrups, and tablets; topical preparations; vaginal tablets). Also included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Acacia; tragacanth; xanthan gum.

18 Comments

Synthetic derivatives of guar gum such as guar acetate, guar phthalate, guar acetate phthalate, oxidized guar gum, and sodium carboxymethyl guar, have also been investigated for their pharmaceutical applications. In particular, sodium carboxymethyl guar gives a transparent gel and, when poured over a pool of mercury, produces a flexible, clear, transparent film. Sodium carboxymethyl guar has been used as a polymer matrix in transdermal patches.(18)

A specification for guar gum is contained in the Food Chemicals Codex (FCC).

The EINECS number for guar gum is 232-536-8.

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21 Authors

AH Kibbe.

22 Date of Revision

12 August 2005.

Hectorite

1 Nonproprietary Names

None adopted.

2 Synonyms

Hector clay; *Hectabrite AW*; *Hectabrite DP*; *Ghassoulite*; *Laponite*; *SHCa-1*; *Strese & Hofmann's Hectorite*.

3 Chemical Name and CAS Registry Number

Hectorite [12173-47-6]

4 Empirical Formula and Molecular Weight

$\approx Na_{0.3}(Mg,Li)_3Si_4O_{10}(F,OH)_2$ ≈ 383

Hectorite is a naturally occurring phyllosilicate clay of the smectite (montmorillonite) group and is a principal component of bentonite clay. Hectorite is a mineral with an approximate empirical formula owing to the variability in cation substitution; *see* Table I.

Table I: Approximate composition of hectorite based on chemical analysis.

Component	Wt %
SiO_2	53.68
Al_2O_3	0.6
MgO	25.34
CaO	0.52
Li_2O	1.12
Na_2O	3.00
K_2O	0.07
Cl^-	0.31
H_2O^+	8.24
H_2O^-	7.28

5 Structural Formula

Hectorite is a natural mineral clay, obtained from altered volcanic ash with a high silica content. It is composed of two tetrahedral layers formed by phyllosilicate sheets and one octahedral layer. The apical oxygens of the two tetrahedral sheets project into the octahedral sheet. It is structurally similar to talc but differs by substitution, mainly in the octahedral layer. Common impurities include aluminum, calcium, chlorine, iron, potassium, and titanium.

See Section 4.

6 Functional Category

Adsorbent; cosmetic ingredient; emulsifying agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Hectorite is used widely in pharmaceutical preparations as an absorbent, emulsifier, stabilizer, suspending agent, thickener, and viscosity-controlling agent.(1)

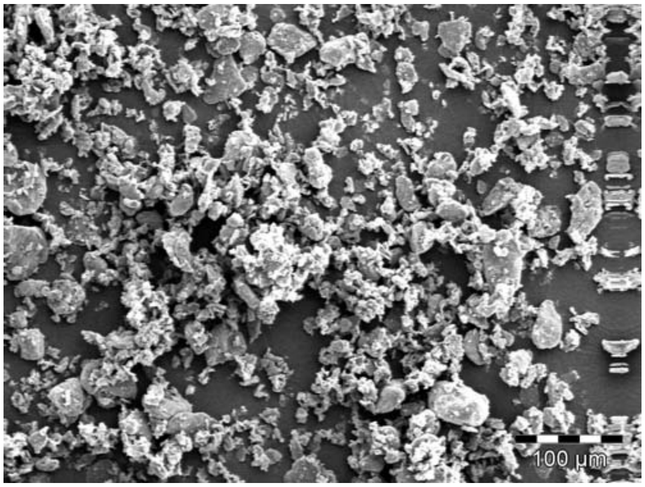
Hectorite is a component of other naturally occurring clays and hence may be suitable for use in similar pharmaceutical formulation applications as an adsorbent, oil-in-water emulsifying agent, suspending agent, or viscosity-increasing agent. It is also available as a synthetic material. Hectorite is used to modify the thixotropic behavior of pharmaceutical dispersions(2) and for stabilizing oil-in-water emulsion bases.(3,4) When combined with an appropriate cation, hectorite exhibits properties suitable for use as a contrast agent.(5)

8 Description

Hectorite occurs as an odorless, white to cream-colored, waxy, dull powder composed of aggregates of colloidal-sized lath-shaped crystals.

SEM: 1

Excipient: Hectorite (*Hectabrite DP*)
Manufacturer: American Colloid Co.
Lot No.: 58905 NFT 288
Magnification: 500×



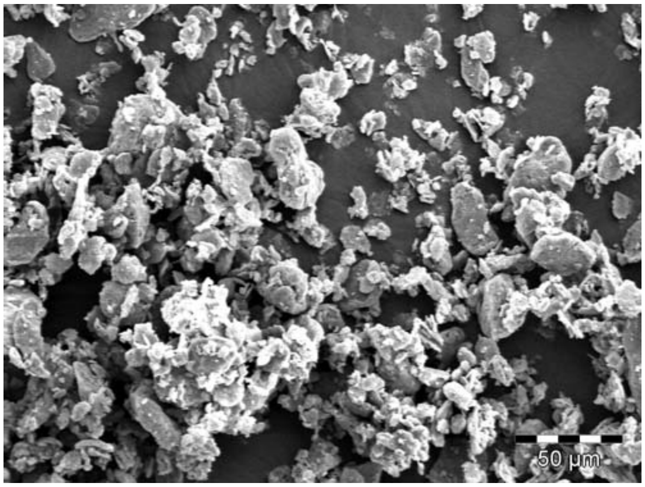
9 Pharmacopeial Specifications

—

10 Typical Properties

Cation exchange capacity: 43.9 meq/100 g
Crystal data: space group C2/*m*, *a* = 5.2, *b* = 9.16, *c* = 16.0, β ≈ 99°.
Density (true): 2.5 g/cm^3

SEM: 2
Excipient: Hectorite (*Hectabrite DP*)
Manufacturer: American Colloid Co.
Lot No.: 58905 NFT 288
*Magnification:*1000×



Hardness (Mohs): 1–2

Moisture content: hectorite loses ≈10% of water up to 150°C; ≈2% above 150°C.

Refractive index: $n = 1.500$

Specific surface area: 63.2 m^2/g. Hectorite swells on the addition of water.

11 Stability and Storage Conditions

Hectorite is a stable material and should be stored in a cool, dry place.

12 Incompatibilities

Contact between hectorite and hydrofluoric acid may generate heat.

13 Method of Manufacture

Naturally occurring hectorite is mined from weathered bentonite deposits. It is further processed to remove grit and impurities so that it is suitable for pharmaceutical and cosmetic applications.

14 Safety

Hectorite is a natural clay mineral that is not considered acutely toxic, therefore no toxicity values have been established. However, hectorite may contain small amounts of crystalline silica in the form of quartz.

Dust can be irritating to the respiratory tract and eyes,(6) and contact with this material may cause drying of the skin. Chronic exposure to crystalline silica may have adverse effects on the respiratory system. EU labeling states that the material is not classified as dangerous.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material being handled. Avoid generating and breathing dust and use eye protection. For dusty conditions, eye protection, gloves, and a dust mask are recommended. The occupational exposure limits for hectorite are 5 mg/m^3 (respirable) PEL-TWA, 3 mg/m^3 (respirable) TLV-TWA, and 10 mg/m^3 (inhalable dust) TLV-TWA.

16 Regulatory Status

Reported in the EPA TSCA Inventory.

17 Related Substances

Attapulgite; bentonite; kaolin; magnesium aluminum silicate; quaternium 18-hectorite; saponite; stearalkonium hectorite; talc.

Quaternium 18-hectorite

CAS numbers: [71011-27-3]; [12001-31-9].

Synonyms: *Bentone 38.*

Comments: quaternium 18-hectorite is used in cosmetics as a viscosity-controlling agent. It does not contain crystalline silica. The EINECS numbers for quaternium 18-hectorite are 234-406-6, and 234-406-6.

Stearalkonium hectorite

CAS numbers: [94891-33-5]; [71011-26-2].

Synonyms: *Bentone 27.*

Comments: steralkonium hectorite is used in cosmetics as a viscosity-controlling agent. The EINECS numbers for stearalkonium hectorite are 305-633-9, and 275-126-4.

18 Comments

Polyethylene glycols 400, 1500, and 4000 have been shown to increase the consistency of hectorite dispersions.(7)

The EINECS number for hectorite is 235-340-0.

19 Specific References

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21 Authors

PE Luner.

22 Date of Revision

23 August 2005.

Heptafluoropropane (HFC)

1 Nonproprietary Names

None adopted.

2 Synonyms

HFA227; HFC227; *Dymel 227 EA/P*; 2-hydroperfluoropropane; P-227; propellant 227; R-227; *Solkane 227*; *Zephex 227 EA*.

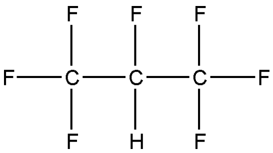
3 Chemical Name and CAS Registry Number

1,1,1,2,3,3,3-Heptafluoropropane [431-89-0]

4 Empirical Formula and Molecular Weight

C_3HF_7 170.0

5 Structural Formula



6 Functional Category

Aerosol propellant.

7 Applications in Pharmaceutical Formulation or Technology

Heptafluoropropane (P-227) is classified as a hydrofluorocarbon (HFC) aerosol propellant since the molecule consists only of carbon, fluorine, and hydrogen atoms. It does not contain any chlorine and consequently does not affect the ozone layer, nor does it have an effect upon global warming. It is therefore considered as an alternative propellant to CFCs for metered-dose inhalers (MDIs). While some of its physical and chemical properties are known, little has been published in regard to its use as a replacement for CFCs in MDIs.

The vapor pressure of heptafluoropropane (P-227) is somewhat lower than that of tetrafluoroethane and dichlorodifluoromethane but considerably higher than the vapor pressure used to formulate most MDIs.

When heptafluoropropane (P-227) is used for pharmaceutical aerosols and MDIs, the pharmaceutical grade must be specified. Industrial grades may not be suitable due to their impurity profile.

Similarly to tetrafluoroethane, heptafluoropropane is not a good solvent for medicinal agents or for the commonly used surfactants and dispersing agents used in the formulation of MDIs.

There are several MDIs formulated with this propellant worldwide that contain a steroid as the active ingredient. A great deal of work is being carried out in regard to its use as a propellant for MDIs.

8 Description

Heptafluoropropane is a liquefied gas and exists as a liquid at room temperature when contained under its own vapor pressure, or as a gas when exposed to room temperature and atmospheric pressure. The liquid is practically odorless and colorless. The gas in high concentration has a faint etherlike odor. Heptafluoropropane is noncorrosive, nonirritating, and nonflammable.

9 Pharmacopeial Specifications

—

10 Typical Properties

Boiling point: −16.5°C
Density:
1.415 g/cm^3 for liquid at 20°C;
1.323 g/cm^3 for liquid at 40°C.
Flammability: nonflammable.
Freezing point: −131°C
Solubility: soluble 1 in 1725 parts of water at 20°C.
Surface tension: 6.96 mN/m at 20°C

11 Stability and Storage Conditions

Heptafluoropropane is a nonreactive and stable material. The liquefied gas is stable when used as a propellant and should be stored in a metal cylinder in a cool, dry place.

12 Incompatibilities

—

13 Method of Manufacture

—

14 Safety

Heptafluoropropane is used as a fire extinguisher and is applicable as a non-CFC propellant in various metered-dose inhalers. Heptafluoropropane is regarded as nontoxic and nonirritating when used as directed. No acute or chronic hazard is present when it is used normally. Inhaling high concentrations of heptafluoropropane vapors can be harmful and is similar to inhaling vapors of other propellants. Deliberate inhalation of vapors of heptafluoropropane can be dangerous and may cause death. The same labeling required of CFC aerosols would be required for those containing heptafluoropropane as a propellant (except for the EPA requirement). (*See* Chlorofluorocarbons (CFC), Section 14.)

15 Handling Precautions

Heptafluoropropane is usually encountered as a liquefied gas and appropriate precautions for handling such materials should be taken. Eye protection, gloves, and protective clothing are recommended. Heptafluoropropane should be handled in a well-ventilated environment. The vapors are heavier than air and do not support life; therefore, when cleaning large tanks that have contained this propellant, adequate provisions for oxygen supply in the tanks must be made in order to protect workers cleaning the tanks. Although nonflammable, when heated to decomposition heptafluoropropane will emit hydrogen fluoride and carbon monoxide.

16 Regulatory Status

—

17 Related Substances

Difluoroethane; tetrafluoroethane.

18 Comments

The main disadvantage of using heptafluoropropane is its lack of miscibility with water and its poor solubility characteristics when used with medicinal agents and the commonly used MDI surfactants.

The use of heptafluoropropane as a propellant for MDIs has been the subject of many patents throughout the world. These patents cover the formulation of MDIs, the use of specific surfactants and cosolvents, etc., and the formulator is referred to the patent literature prior to formulating an MDI with any HFC as the propellant. The formulation of MDIs with tetrafluoroethane and heptafluoropropane propellant is complicated since they may serve as a replacement for dichlorodifluoromethane or dichlorotetrafluoroethane. The use of an HFC as the propellant also requires a change in manufacturing procedure, which necessitates a redesign of the filling and packaging machinery for an MDI.

19 Specific References

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20 General References

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21 Authors

CJ Sciarra, JJ Sciarra.

22 Date of Revision

23 August 2005.

Hexetidine

1 Nonproprietary Names

BP: Hexetidine
PhEur: Hexetidinum

2 Synonyms

5-Amino-1,3-bis(2-ethylhexyl)hexahydro-5-methylpyrimidine; 5-amino-1,3-di(β-ethylhexyl)hexahydro-5-methylpyrimidine; 1,3-bis(2-ethylhexyl)-5-methylhexahydropyrimidin-5-ylamine; 1,3-bis(β-ethylhexyl)-5-methyl-5-aminohexahydropyrimidine; *Glypesin*; *Hexigel*; *Hexocil*; *Hexoral*; *Hextril*; *Oraldene*; *Sterisil*; *Steri/Sol.*

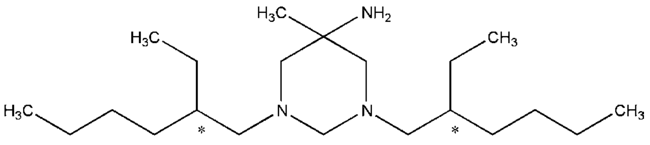
3 Chemical Name and CAS Registry Number

1,3-bis(2-Ethylhexyl)-5-methylhexahydro-5-pyrimidinamine
[141-94-6]

4 Empirical Formula and Molecular Weight

$C_{21}H_{45}N_3$ 339.61

5 Structural Formula



Mixture of stereoisomers

6 Functional Category

Antimicrobial preservative; antiseptic.

7 Applications in Pharmaceutical Formulation or Technology

Hexetidine is used as an antimicrobial preservative in cosmetics and nonparenteral pharmaceutical formulations. Therapeutically, hexetidine is mainly used as a 0.1% w/v solution in mouthwash formulations for the prevention and treatment of minor local infections, gingivitis, and mouth ulcers.

8 Description

Hexetidine is a colorless or faint yellow-colored oily liquid with a characteristic amine odor.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for hexetidine.

Test	PhEur 2005
Identification	+
Characters	+
Relative density	0.864–0.870
Refractive index	1.461–1.467
Optical rotation	−0.10° to +0.10°
Absorbance	+
Related substances	+
Sulfated ash	⩽0.1%
Heavy metals	⩽10 ppm
Assay	98.0–102.0%

10 Typical Properties

Antimicrobial activity: hexetidine is a nonantibiotic antimicrobial agent that possesses broad-spectrum antimicrobial activity against Gram-positive and Gram-negative bacteria and fungi such as *Candida albicans*.(1–4) Several studies have identified the antiplaque activity of hexetidine.(3–8) Hexetidine has been shown to be effective against isolates of *Staphylococcus aureus* and *Pseudomonas aeruginosa* in planktonic form and against biofilms of the same microorganisms on PVC.(1) Hexetidine has also been reported to reduce the adherence of *Candida albicans* to human buccal epithelial cells *in vitro*.(9) Hexetidine has been shown to be a promising candidate antimalarial agent, with IC_{50} values being comparable with those of quinine chlorohydrate and chloroquine sulfate.(10) *See also* Table II.

Boiling point: 172–176°C

Dissociation constant: $pK_a = 8.3$

Density: 0.864–0.870 at 20°C

Refractive index: $n_D^{20} = 1.463–1.467$

Solubility: soluble in acetone, benzene, chloroform, dichloromethane, ethanol (95%), *n*-hexane, methanol, mineral acids, petroleum ether, and propylene glycol; very slightly soluble in water.

Table II: Minimum inhibitory concentrations (MICs) for hexetidine.

Microorganism	MIC (μg/mL)
Aspergillus niger	<25
Bacillus subtilis	<25
Candida albicans	250–500
Escherichia coli	>500
Pseudomonas aeruginosa	>500
Staphylococcus aureus	>25
Staphylococcus epidermitis	>6

11 Stability and Storage Conditions

Hexetidine is stable and should be stored in a well-closed container in a cool, dry place. Brass and copper equipment should not be used for the handling or storage of hexetidine.

12 Incompatibilities

Hexetidine is incompatible with strong oxidizing agents. Salts are formed with mineral and organic acids; strong acids cause opening of the hexahydropyrimidine ring, releasing formaldehyde.

13 Method of Manufacture

Hexetidine is prepared by hydrogenation under pressure of 1,3-bis(2-ethylhexyl)-5-methyl-4-nitrohexahydropyriminine at 100°C using Raney nickel as a catalyst.

14 Safety

Hexetidine is mainly used in mouthwashes as a bactericidal and fungicidal antiseptic. It is also used as an antimicrobial preservative and is generally regarded as a relatively nontoxic and nonirritant material at concentrations up to 0.1% w/v. Allergic contact dermatitis and altered olfactory and taste perception have occasionally been reported. Hexetidine is toxic when administered intravenously.

Solutions of hexetidine in oil at concentrations of 5–10% w/v cause strong primary irritations without sensitization in humans. Long-term toxicological studies of up to 0.1% w/w of hexetidine in food for 1 year do not show any toxic effect. Fetotoxicity, embryotoxicity, and teratogenicity studies in rats of doses up to 50 mg/kg/day exhibit no sign of toxicity.

LD_{100} (cat, IV): 5–20 mg/kg
LD_{50} (dog, oral): 1.60 g/kg
LD_{50} (mouse, IP): 0.142 g/kg
LD_{50} (mouse, oral): 1.52 g/kg
LD_{50} (rat, oral): 0.61–1.43 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hexetidine may be harmful upon inhalation or on contact with the skin or eyes. Eye protection and gloves are recommended. When significant quantities are being handled, the use of a respirator with an appropriate gas filter is recommended.

16 Regulatory Status

Included in nonparenteral formulations licensed in Europe.

17 Related Substances

—

18 Comments

Hexetidine has been quantitatively determined in both commercial formulations and saliva using a reversed-phase HPLC method,(11) with determination being possible at concentrations below the published minimum inhibitory concentrations for a selection of microorganisms.

The EINECS number for hexetidine is 205-513-5.

19 Specific References

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2 Guiliana G, Pizzo G, Milici ME, Giangreco R. *In vitro* activities of antimicrobial agents against *Candida* species. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; **87**(1): 44–49.

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8 Sharma NC, Galustians HJ, Qaqish J, *et al.* Antiplaque and antigingivitis effectiveness of a hexetidine mouthwash. *J Clin Periodontol* 2003; **30**(7): 590–594.

9 Jones DS, McGovern JG, Woolfson AD, Gorman SP. The effects of hexetidine (Oraldene) on the adherence of *Candida albicans* to human buccal epithelial cells *in vitro* and *ex vivo* and on *in vitro* morphogenesis. *Pharm Res* 1997; **14**(12): 1765–1771.

10 Gozalbes R, Galvez J, Moreno A, Garcia-Domenech R. Discovery of new antimalarial compounds by use of molecular connectivity techniques. *J Pharm Pharmacol* 1999; **51**(2): 111–117.

11 McCoy CP, Jones DS, McGovern JG, *et al.* Determination of the salivary retention of hexetidine in-vivo by high-performance liquid chromatography. *J Pharm Pharmacol* 2000; **52**(11): 1355–1359.

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Jones DS, McGovern JG, Woolfson AD, *et al.* Physicochemical characterization of hexetidine-impregnated endotracheal tube poly(vinyl chloride) and resistance to adherence of respiratory bacterial pathogens. *Pharm Res* 2002; **19**(6): 818–824.

21 Authors

DS Jones, CP McCoy.

22 Date of Revision

17 August 2005.

Hydrocarbons (HC)

1 Nonproprietary Names

(a) USPNF: Butane
(b) USPNF: Isobutane
(c) USPNF: Propane

2 Synonyms

(a) A-17; *Aeropres 17*; *n*-butane; E943a
(b) A-31; *Aeropres 31*; E943b; 2-methylpropane
(c) A-108; *Aeropres 108*; dimethylmethane; E944; propyl hydride

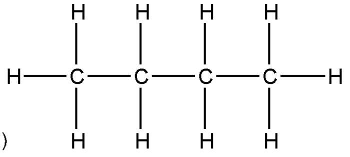
3 Chemical Name and CAS Registry Number

(a) Butane [106-97-8]
(b) 2-Methylpropane [75-28-5]
(c) Propane [74-98-6]

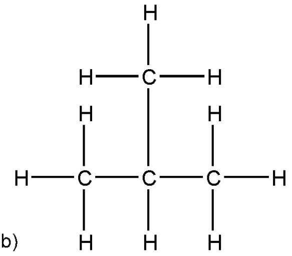
4 Empirical Formula and Molecular Weight

(a)	C_4H_{10}	58.12
(b)	C_4H_{10}	58.12
(c)	C_3H_8	44.10

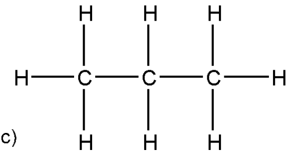
5 Structural Formula



(a) Butane



(b) Isobutane



(c) Propane

6 Functional Category

Aerosol propellant.

7 Applications in Pharmaceutical Formulation or Technology

Propane, butane, and isobutane are hydrocarbons (HC). They are used as aerosol propellants: alone, in combination with each other, and in combination with a hydrofluoroalkane (HFA) propellant. They are used primarily in topical pharmaceutical aerosols (particularly aqueous foam and some spray products).

Depending upon the application, the concentration of hydrocarbon propellant range is 5–95% w/w. Foam aerosols generally use about 4–5% w/w of a hydrocarbon propellant consisting of isobutane (84.1%) and propane (15.9%), or isobutane alone. Spray-type aerosols utilize propellant concentrations of 50% w/w and higher.(1)

Hydrocarbon propellants are also used in cosmetics and food products as aerosol propellants.

Only highly purified hydrocarbon grades can be used for pharmaceutical formulations since they may contain traces of unsaturated compounds that not only contribute a slight odor to a product but may also react with other ingredients.

8 Description

Hydrocarbon propellants are liquefied gases and exist as liquids at room temperature when contained under their own vapor pressure, or as gases when exposed to room temperature and atmospheric pressure. They are essentially clear, colorless, odorless liquids but may have a slight etherlike odor.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for hydrocarbons from the USPNF 23.

Test	Butane	Isobutane	Propane
Identification	+	+	+
Water	⩽0.001%	⩽0.001%	⩽0.001%
High-boiling residues	⩽5 μg/mL	⩽5 μg/mL	⩽5 μg/mL
Acidity of residue	+	+	+
Sulfur compounds	+	+	+
Assay	⩾97.0%	⩾95.0%	⩾98.0%

10 Typical Properties

See Table II for selected typical properties.

11 Stability and Storage Conditions

Butane and the other hydrocarbons used as aerosol propellants are stable compounds and are chemically nonreactive when used as propellants. They are, however, highly flammable and explosive when mixed with certain concentrations of air; *see* Section 10.(2) They should be stored in a well-ventilated area, in a tightly sealed cylinder. Exposure to excessive heat should be avoided.

Table II: Selected typical properties for hydrocarbon propellants.

	Butane	Isobutane	Propane
Autoignition temperature	405°C	420°C	468°C
Boiling point	−0.5°C	−11.7°C	–42.1°C
Critical pressure	3.80 MPa (37.47 atm)	3.65 MPa (36 atm)	4.26 MPa (42.01 atm)
Critical temperature	152°C	135°C	96.8°C
Density: liquid at 20°C	0.58 g/cm^3	0.56 g/cm^3	0.50 g/cm^3
Explosive limits			
Lower limit	1.9% v/v	1.8% v/v	2.2% v/v
Upper limit	8.5% v/v	8.4% v/v	9.5% v/v
Flash point	−62°C	−83°C	−104.5°C
Freezing point	−138.3°C	−159.7°C	−187.7°C
Kauri-butanol value	19.5	17.5	15.2
Vapor density			
Absolute	2.595 g/m^3	2.595 g/m^3	1.969 g/m^3
Relative	2.046 (air = 1)	2.01 (air = 1)	1.53 (air = 1)
Vapor pressure at 21°C	113.8 kPa (16.5 psig)	209.6 kPa (30.4 psig)	758.4 kPa (110.0 psig)
Vapor pressure at 54.5°C	—	661.9 kPa (96.0 psig)	1765.1 kPa (256 psig)

12 Incompatibilities

Other than their lack of miscibility with water, butane and the other hydrocarbon propellants do not have any practical incompatibilities with the ingredients commonly used in pharmaceutical aerosol formulations. Hydrocarbon propellants are generally miscible with nonpolar materials and some semipolar compounds such as ethanol.

13 Method of Manufacture

Butane and isobutane are obtained by the fractional distillation, under pressure, of crude petroleum and natural gas. They may be purified by passing through a molecular sieve to remove any unsaturated compounds that are present.

Propane is prepared by the same method. It may also be prepared by a variety of synthetic methods.

14 Safety

The hydrocarbons are not generally regarded as toxic materials when used as aerosol propellants. However, deliberate inhalation of aerosol products containing hydrocarbon propellants can be fatal.

15 Handling Precautions

Butane and the other hydrocarbon propellants are liquefied gases and should be handled with appropriate caution. Direct contact of liquefied gas with the skin is hazardous and may result in serious cold burn injuries. Protective clothing, rubber gloves, and eye protection are recommended.

Butane, isobutane, and propane are asphyxiants and should be handled in a well-ventilated environment; it is recommended that environmental oxygen levels are monitored and not permitted to fall below a concentration of 18% v/v. These vapors do not support life; therefore when cleaning large tanks, adequate provisions for oxygen supply must be provided for personnel cleaning the tanks. Butane is highly flammable and explosive and must only be handled in an explosion-proof room that is equipped with adequate safety warning devices and explosion-proof equipment.

To fight fires, the flow of gas should be stopped and dry powder extinguishers should be used.

16 Regulatory Status

GRAS listed. Butane, isobutane, and propane are accepted for use as food additives in Europe. Included in the FDA Inactive Ingredients Guide (aerosol formulations for topical application). Included in nonparental medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Dimethyl ether.

18 Comments

Although hydrocarbon aerosol propellants are relatively inexpensive, nontoxic, and environmentally friendly (since they are not damaging to the ozone layer and are not greenhouse gases), their use is limited by their flammability. While hydrocarbon propellants are primarily used in topical aerosol formulations, it is possible that butane may also be useful in metered-dose inhalers as a replacement for chlorofluorocarbons.

Various blends of hydrocarbon propellants that have a range of physical properties suitable for different applications are commercially available, e.g., *CAP30* (Calor Gas Ltd.) is a mixture of 11% propane, 29% isobutane, and 60% butane. A-46 (*Aeropres*) is a commonly used mixture for aerosol foams and consists of about 85% isobutane and 15% propane. The number following the letter denotes the approximate vapor pressure of the blend or mixture.

19 Specific References

1 Sciarra JJ. Pharmaceutical aerosols. In: Banker GS, Rhodes CT, eds. *Modern Pharmaceutics*, 3rd edn. New York: Marcel Dekker, 1996: 547–574.

2 Dalby RN. Prediction and assessment of flammability hazards associated with metered-dose inhalers containing flammable propellants. *Pharm Res* 1992; 9: 636–642.

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21 Authors

CJ Sciarra, JJ Sciarra.

22 Date of Revision

23 August 2005.

Hydrochloric Acid

1 Nonproprietary Names

BP: Hydrochloric acid
JP: Hydrochloric acid
PhEur: Acidum hydrochloridum concentratum
USPNF: Hydrochloric acid

2 Synonyms

Chlorohydric acid; concentrated hydrochloric acid; E507.

3 Chemical Name and CAS Registry Number

Hydrochloric acid [7647-01-0]

4 Empirical Formula and Molecular Weight

HCl 36.46

5 Structural Formula

HCl

6 Functional Category

Acidifying agent.

7 Applications in Pharmaceutical Formulation or Technology

Hydrochloric acid is widely used as an acidifying agent, in a variety of pharmaceutical and food preparations (*see* Section 16). It may also be used to prepare dilute hydrochloric acid, which in addition to its use as an excipient has some therapeutic use, intravenously in the management of metabolic alkalosis, and orally for the treatment of achlorhydria. *See* Section 17.

8 Description

Hydrochloric acid occurs as a clear, colorless, fuming aqueous solution of hydrogen chloride, with a pungent odor.

The JP 2001 specifies that hydrochloric acid contains 35.0–38.0% w/w of HCl; the PhEur 2005 specifies that hydrochloric acid contains 35.0–39.0% w/w of HCl; and the USPNF 23 specifies that hydrochloric acid contains 36.5–38.0% w/w of HCl. *See also* Section 9.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for hydrochloric acid.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	+	+	—
Appearance of solution	—	+	—
Residue on ignition	$\leqslant$1.0 mg	—	$\leqslant$0.008%
Residue on evaporation	—	$\leqslant$0.01%	—
Bromide or iodide	+	—	+
Free bromine	+	—	+
Free chlorine	+	$\leqslant$4 ppm	+
Sulfate	+	$\leqslant$20 ppm	+
Sulfite	+	—	+
Arsenic	$\leqslant$1 ppm	—	—
Heavy metals	$\leqslant$5 ppm	$\leqslant$2 ppm	$\leqslant$5 ppm
Mercury	$\leqslant$0.04 ppm	—	—
Assay (of HCl)	35.0–38.0%	35.0–39.0%	36.5–38.0%

10 Typical Properties

Acidity/alkalinity: pH = 0.1 (10% v/v aqueous solution)
Boiling point: 110°C (constant boiling mixture of 20.24% w/w HCl)
Density: $\approx$1.18 g/cm^3 at 20°C
Freezing point: ≈ -24°C
Refractive index: $n_D^{20} = 1.342$ (10% v/v aqueous solution)
Solubility: miscible with water; soluble in diethyl ether, ethanol (95%), and methanol.

11 Stability and Storage Conditions

Hydrochloric acid should be stored in a well-closed, glass or other inert container at a temperature below 30°C. Storage in close proximity to concentrated alkalis, metals, and cyanides should be avoided.

12 Incompatibilities

Hydrochloric acid reacts violently with alkalis, with the evolution of a large amount of heat. Hydrochloric acid also reacts with many metals, liberating hydrogen.

13 Method of Manufacture

Hydrochloric acid is an aqueous solution of hydrogen chloride gas produced by a number of methods including: the reaction of sodium chloride and sulfuric acid; the constituent elements; as a by-product from the electrolysis of sodium hydroxide; and as a by-product during the chlorination of hydrocarbons.

14 Safety

When used diluted, at low concentration, hydrochloric acid is not usually associated with any adverse effects. However, the concentrated solution is corrosive and can cause severe damage on contact with the eyes and skin, or if ingested.

LD$_{50}$ (mouse, IP): 1.4 g/kg(1)
LD$_{50}$ (rabbit, oral): 0.9 g/kg

15 Handling Precautions

Caution should be exercised when handling hydrochloric acid and suitable protection against inhalation and spillage should be taken. Eye protection, gloves, face mask, apron, and respirator are recommended, depending on the circumstances and quantity of hydrochloric acid handled. Spillages should be diluted with copious amounts of water and run to waste. Splashes on the skin and eyes should be treated by immediate and prolonged washing with large amounts of water and medical attention should be sought. Fumes can cause irritation to the eyes, nose, and respiratory system; prolonged exposure to fumes may damage the lungs. In the UK, the recommended short-term exposure limit for hydrogen chloride gas and aerosol mists is 8 mg/m^3 (5 ppm). The long-term exposure limit (8-hour TWA) is 2 mg/m^3 (1 ppm).(2)

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (dental solutions; epidural injections, IM, IV, and SC injections, inhalations, ophthalmic preparations, oral solutions, nasal, otic, rectal, and topical preparations). Included in parenteral and nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Dilute hydrochloric acid.

Dilute hydrochloric acid

Synonyms: acidum hydrochloridum dilutum; diluted hydrochloric acid.

Density: ≈1.05 g/cm^3 at 20°C

Comments: the JP 2001 and PhEur 2005 specify that dilute hydrochloric acid contains 9.5–10.5% w/w of HCl and is prepared by mixing 274 g of hydrochloric acid with 726 g of water. The USPNF 23 specifies 9.5–10.5% w/v of HCl, prepared by mixing 226 mL of hydrochloric acid with sufficient water to make 1000 mL.

18 Comments

In pharmaceutical formulations, dilute hydrochloric acid is usually used as an acidifying agent in preference to hydrochloric acid. Hydrochloric acid is also used therapeutically as an escharotic.(3) The PhEur 2005 also contains a specification for hydrochloric acid, dilute; *see* Section 17.

A specification for hydrochloric acid is contained in the Food Chemicals Codex (FCC).

The EINECS number for hydrochloric acid is 231-595-7.

19 Specific References

1 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 1980.

2 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002.* Sudbury: Health and Safety Executive, 2002.

3 Sweetman S, ed. *Martindale: The Complete Drug Reference*, 34th edn. London: Pharmaceutical Press, 2005: 1699.

20 General References

Japan Pharmaceutical Excipients Council. *Japanese Pharmaceutical Excipients Directory 1996*. Tokyo: Yakuji Nippo, 1996: 228.

21 Authors

SC Owen.

22 Date of Revision

12 August 2005.

Hydroxyethyl Cellulose

1 Nonproprietary Names

BP: Hydroxyethylcellulose
PhEur: Hydroxyethylcellulosum
USPNF: Hydroxyethyl cellulose

2 Synonyms

Cellosize HEC; cellulose hydroxyethyl ether; cellulose hydroxyethylate; ethylhydroxy cellulose; ethylose; HEC; HE cellulose; 2-hydroxyethyl cellulose ether; hydroxyethyl ether cellulose; hydroxyethyl starch; hyetellose; *Natrosol*; oxycellulose; *Tylose PHA*.

3 Chemical Name and CAS Registry Number

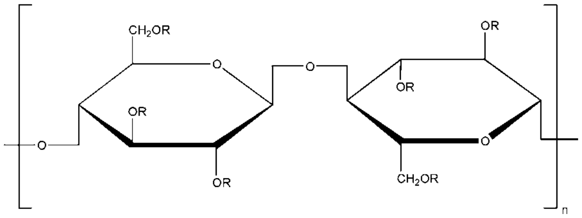
Cellulose, 2-hydroxyethyl ether [9004-62-0]

4 Empirical Formula and Molecular Weight

The USPNF 23 describes hydroxyethyl cellulose as a partially substituted poly(hydroxyethyl) ether of cellulose. It is available in several grades that vary in viscosity and degree of substitution; some grades are modified to improve their dispersion in water. The grades are distinguished by appending a number indicative of the apparent viscosity in mPa s, of a 2% w/v solution measured at 20°C. Hydroxyethyl cellulose may also contain a suitable anticaking agent.

See Section 10.

5 Structural Formula



where R is H or $[\text{—}CH_2CH_2O\text{—}]_mH$

6 Functional Category

Coating agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Hydroxyethyl cellulose is a nonionic, water-soluble polymer widely used in pharmaceutical formulations. It is primarily used as a thickening agent in ophthalmic(1) and topical formulations,(2) although it is also used as a binder(3) and film-coating agent for tablets.(4) It is present in lubricant preparations for dry eye, contact lens care, and dry mouth.(5)

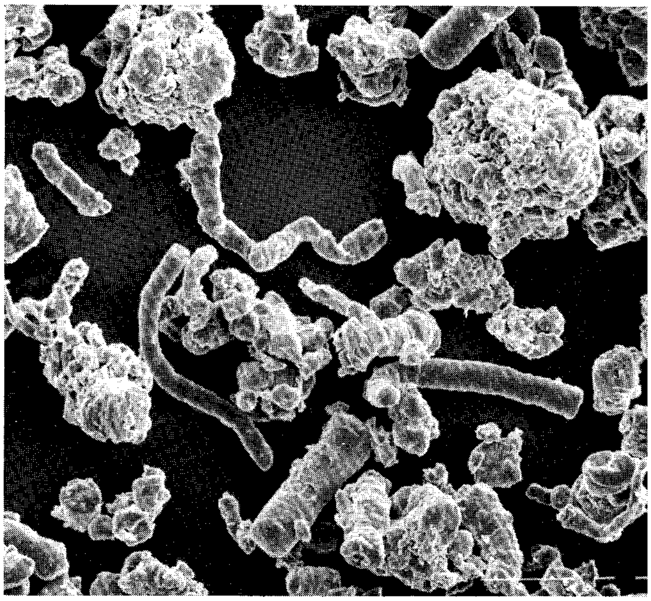
The concentration of hydroxyethyl cellulose used in a formulation is dependent upon the solvent and the molecular weight of the grade.

Hydroxyethyl cellulose is also widely used in cosmetics.

8 Description

Hydroxyethyl cellulose occurs as a light tan or cream to white-colored, odorless and tasteless, hygroscopic powder.

SEM: 1
Excipient: Hydroxyethyl cellulose (*Natrosol*)
Manufacturer: Aqualon
Magnification: 120×



9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acidity/alkalinity: pH = 5.5–8.5 for a 1% w/v aqueous solution.

Ash:
2.5% w/w for *Cellosize*;
3.5% w/w for *Natrosol.*

Autoignition temperature: 420°C

Density (bulk):
0.35–0.61 g/cm^3 for *Cellosize*;
0.60 g/cm^3 for *Natrosol.*

Melting point: softens at 135–140°C, decomposes at about 205°C.

SEM: 2
Excipient: Hydroxyethyl cellulose (*Natrosol*)
Manufacturer: Aqualon
Magnification: 600×

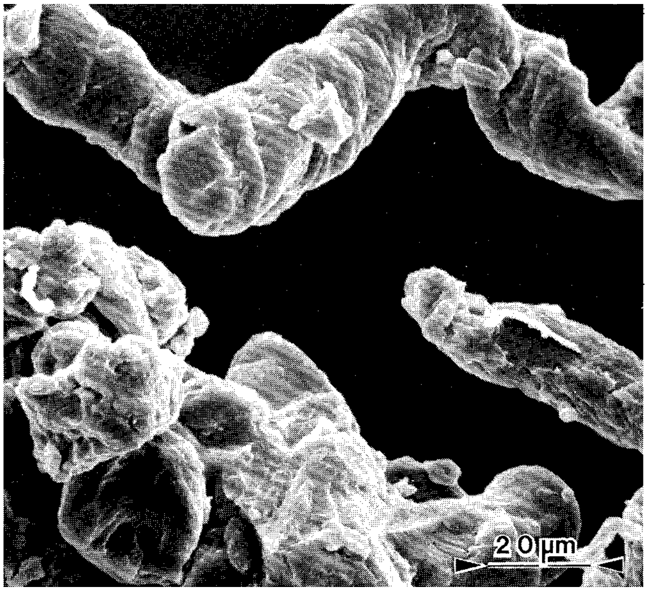


Table I: Pharmacopeial specifications for hydroxyethyl cellulose

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Viscosity	75.0–140.0%	+
pH	5.5–8.5	6.0–8.5
Loss on drying	⩽10.0%	⩽10.0%
Lead	—	⩽0.001%
Residue on ignition	⩽4.0%	⩽5.0%
Chlorides	⩽1.0%	—
Heavy metals	⩽20 ppm	⩽20 µg/g
Organic volatile impurities	—	+
Nitrates	+	—
Glyoxal	⩽20 ppm	—
Ethylene oxide	⩽1 ppm	—
2-Chloroethanol	⩽5 ppm	—
Nitrates	+	—

Moisture content: commercially available grades of hydroxyethylcellulose contain less than 5% w/w of water. However, as hydroxyethyl cellulose is hygroscopic, the amount of water absorbed depends upon the initial moisture content and the relative humidity of the surrounding air. Typical equilibrium moisture values for *Natrosol 250* at 25°C are: 6% w/w at 50% relative humidity and 29% w/w at 84% relative humidity.

Particle size distribution:

Cellosize: 100% through a US #80 mesh (177 µm);

Natrosol (regular grind): 10% retained on a US #40 mesh (420 µm);

Natrosol (X-grind): 0.5% retained on a US #60 mesh (250 µm).

Refractive index: $n_D^{20} = 1.336$ for a 2% w/v aqueous solution.

Solubility: hydroxyethyl cellulose is soluble in either hot or cold water, forming clear, smooth, uniform solutions. Practically insoluble in acetone, ethanol (95%), ether, toluene, and most other organic solvents. In some polar organic solvents, such as the glycols, hydroxyethyl cellulose either swells or is partially soluble.

Specific gravity: 1.38–1.40 for *Cellosize*; 1.0033 for a 2% w/v aqueous hydroxyethyl cellulose solution.

Surface tension: *see* Table II.

Table II: Surface tension (mN/m) of different *Cellosize* (Amerchol Corp.) grades at 25°C

Concentration of aqueous solution (% w/v)	*Cellosize* grade					
	WP-02	WP-09	WP-300	QP-4400	QP-52000	QP-100M
0.01	65.8	65.7	66.4	66.3	65.9	66.1
0.1	65.3	65.4	65.8	65.3	65.4	65.4
1.0	64.4	65.1	65.5	65.8	66.1	66.3
2.0	64.2	65.0	66.3	67.3	—	—
5.0	64.1	64.7	—	—	—	—
10.0	64.4	65.9	—	—	—	—

Viscosity (dynamic): hydroxyethyl cellulose is available in a wide range of viscosity types; e.g. *Cellosize* is manufactured in 11 regular viscosity grades. Hydroxyethyl cellulose grades differ principally in their aqueous solution viscosities which range from 2–20 000 mPa s for a 2% w/v aqueous solution. Two types of *Cellosize* are produced, a WP-type, which is a normal-dissolving material, and a QP-type, which is a rapid-dispersing material.

The lowest viscosity grade (02) is available only in the WP-type. Five viscosity grades (09, 3, 40, 300, and 4400) are produced in both WP- and QP-types. Five high-viscosity grades (10000, 15000, 30000, 52000, and 100 M) are produced only in the QP-type.

For the standard *Cellosize* grades and types available and their respective viscosity ranges in aqueous solution, *see* Table III.

Natrosol 250 has a degree of substitution of 2.5 and is produced in 10 viscosity types. The suffix ‘R’ denotes that *Natrosol* has been surface-treated with glyoxal to aid in solution preparation; *see* Table IV.

Aqueous solutions made using a rapidly dispersing material may be prepared by dispersing the hydroxyethyl cellulose in mildly agitated water at 20–25°C. When the hydroxyethyl cellulose has been thoroughly wetted, the temperature of the solution may be increased to 60–70°C to increase the rate of dispersion. Making the solution slightly alkaline also increases the dispersion process. Typically, complete dispersion may be achieved in approximately an hour by controlling the temperature, pH, and rate of stirring.

Normally dispersing grades of hydroxyethyl cellulose require more careful handling to avoid agglomeration during dispersion; the water should be stirred vigorously. Alternatively, a slurry of hydroxyethyl cellulose may be prepared in a nonaqueous solvent, such as ethanol, prior to dispersion in water.

See also Section 11 for information on solution stability.

Table III: Approximate viscosities of various grades of aqueous *Cellosize* (Amerchol Corp.) solutions at 25°C.

Type	Grade	Concentration (% w/v)	Viscosity (mPa s)[a]	
			Low	High
WP	02	5	7–14	14–20
WP and QP	09	5	60–100	100–140
	3	5	220–285	285–350
	40	2	70–110	110–150
	300	2	250–325	325–400
	4400	2	4 200–4 700	700–5 200
QP	10000	2	5 700	6 500
	15000	2	15 000–18 000	18 000–21 000
	30000	1	950–1 230	1 230–1 500
	52000	1	1 500–1 800	1 800–2 100
	100M	1	2 500	3 000

[a] *Cellosize* viscosity grades are available in narrower ranges, as noted by the Low and High designation.

Table IV: Approximate viscosities of various grades of aqueous *Natrosol 250* (Aqualon Inc.) solutions at 25°C.

Type	Viscosity (mPa s) for varying concentrations (% w/v)		
	1%	2%	5%
HHR	3 400–5 000	—	—
H4R	2 600–3 300	—	—
HR	1 500–2 500	—	—
MHR	800–1 500	—	—
MR	—	4 500–6 500	—
KR	—	1 500–2 500	—
GR	—	150–400	—
ER	—	25–105	—
JR	—	—	150–400
LR	—	—	75–150

11 Stability and Storage Conditions

Hydroxyethyl cellulose powder is a stable though hygroscopic material.

Aqueous solutions of hydroxyethyl cellulose are relatively stable at pH 2–12 with the viscosity of solutions being largely unaffected. However, solutions are less stable below pH 5 owing to hydrolysis. At high pH, oxidation may occur.

Increasing the temperature reduces the viscosity of aqueous hydroxyethyl cellulose solutions. However on cooling, the original viscosity is restored. Solutions may be subjected to freeze–thawing, high-temperature storage, or boiling without precipitation or gelation occurring.

Hydroxyethyl cellulose is subject to enzymatic degradation, with consequent loss in viscosity of its solutions.(6) Enzymes that catalyze this degradation are produced by many bacteria and fungi present in the environment. For prolonged storage, an antimicrobial preservative should therefore be added to aqueous solutions. Aqueous solutions of hydroxyethyl cellulose may also be sterilized by autoclaving.

Hydroxyethyl cellulose powder should be stored in a well-closed container, in a cool, dry place.

12 Incompatibilities

Hydroxyethyl cellulose is insoluble in most organic solvents. It is incompatible with zein and partially compatible with the following water-soluble compounds: casein; gelatin; methylcellulose; polyvinyl alcohol, and starch.

Hydroxyethyl cellulose can be used with a wide variety of water-soluble antimicrobial preservatives. However, sodium pentachlorophenate produces an immediate increase in viscosity when added to hydroxyethyl cellulose solutions.

Hydroxyethyl cellulose has good tolerance for dissolved electrolytes, although it may be salted out of solution when mixed with certain salt solutions. For example, the following salt solutions will precipitate a 10% w/v solution of *Cellosize WP-09* and a 2% w/v solution of *Cellosize WP-4400*: sodium carbonate 50% and saturated solutions of aluminum sulfate; ammonium sulfate; chromic sulfate; disodium phosphate; magnesium sulfate; potassium ferrocyanide; sodium sulfate; sodium sulfite; sodium thiosulfate; and zinc sulfate.

Natrosol is soluble in most 10% salt solutions, excluding sodium carbonate and sodium sulfate, and many 50% salt solutions with the exception of the following: aluminum sulfate; ammonium sulfate; diammonium phosphate; disodium phosphate; ferric chloride; magnesium sulfate; potassium ferrocyanide; sodium metaborate; sodium nitrate; sodium sulfite; trisodium phosphate; and zinc sulfate. *Natrosol 150* is generally more tolerant of dissolved salts than is *Natrosol 250*.

Hydroxyethyl cellulose is also incompatible with certain fluorescent dyes or optical brighteners, and certain quaternary disinfectants which will increase the viscosity of aqueous solutions.

13 Method of Manufacture

A purified form of cellulose is reacted with sodium hydroxide to produce a swollen alkali cellulose, which is chemically more reactive than untreated cellulose. The alkali cellulose is then reacted with ethylene oxide to produce a series of hydroxyethyl cellulose ethers.

The manner in which ethylene oxide is added to cellulose can be described by two terms, the degree of substitution (DS) and the molar substitution (MS). The DS designates the average number of hydroxyl positions on the anhydroglucose unit that have been reacted with ethylene oxide. Since each anhydroglucose unit of the cellulose molecule has three hydroxyl groups, the maximum value for DS is 3. MS is defined as the average number of ethylene oxide molecules that have reacted with each anhydroglucose unit. Once a hydroxyethyl group is attached to each unit, it can further react with additional groups in an end-to-end formation. This reaction can continue and there is no theoretical limit for MS.

14 Safety

Hydroxyethyl cellulose is primarily used in ophthalmic and topical pharmaceutical formulations. It is generally regarded as an essentially nontoxic and nonirritant material.(7,8)

Acute and subacute oral toxicity studies in rats have shown no toxic effects attributable to hydroxyethyl cellulose consumption; the hydroxyethyl cellulose being neither absorbed nor hydrolyzed in the rat gastrointestinal tract. However, although used in oral pharmaceutical formulations, hydroxyethyl cellulose has not been approved for direct use in food products; *see* Section 16.

Glyoxal-treated hydroxyethyl cellulose is not recommended for use in oral pharmaceutical formulations or topical preparations that may be used on mucous membranes. Hydroxyethyl cellulose is also not recommended for use in parenteral products.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hydroxyethyl cellulose dust may be irritant to the eyes and eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hydroxyethyl cellulose is combustible.

When heated to decomposition, hydroxyethyl cellulose emits acrid smoke and irritating vapors, in which case a ventilator is recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (ophthalmic preparations; oral syrups and tablets; otic and topical preparations). Included in nonparenteral medicines licensed in the UK.

Hydroxyethyl cellulose is not currently approved for use in food products in Europe or the USA, although it is permitted for use in indirect applications such as packaging. This restriction is due to the high levels of ethylene glycol residues that are formed during the manufacturing process.

17 Related Substances

Hydroxyethylmethyl cellulose; hydroxypropyl cellulose; hypromellose; methylcellulose.

18 Comments

The limited scope for the use of hydroxyethyl cellulose in foodstuffs is in stark contrast to its widespread application as an excipient in oral pharmaceutical formulations.

Hydroxyethyl cellulose hydrogels may also be used in various delivery systems.(9)

19 Specific References

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21 Authors

RJ Harwood.

22 Date of Revision

17 August 2005.

Hydroxyethylmethyl Cellulose

1 Nonproprietary Names

BP: Hydroxyethylmethylcellulose
PhEur: Methylhydroxyethylcellulosum

2 Synonyms

Cellulose, 2-hydroxyethyl methyl ester; *Culminal MHEC*; HEMC; hydroxyethyl methylcellulose; hymetellose; MHEC; methylhydroxyethylcellulose; *Tylopur MH*; *Tylopur MHB*; *Tylose MB*; *Tylose MH*; *Tylose MHB*.

3 Chemical Name and CAS Registry Number

Hydroxyethylmethylcellulose [9032-42-2]

4 Empirical Formula and Molecular Weight

The PhEur 2005 describes hydroxyethylmethyl cellulose as a partly O-methylated and O-(2-hydroxyethylated) cellulose. Various different grades are available, which are distinguished by appending a number indicative of the apparent viscosity in millipascal seconds (mPa s) of a 2% w/v solution measured at 20°C.

5 Structural Formula

See Section 4.

6 Functional Category

Coating agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Hydroxyethylmethyl cellulose is used as an excipient in a wide range of pharmaceutical products, including oral tablets and suspensions and topical gel preparations.(1) It has similar properties to methylcellulose, but the hydroxyethyl groups make it more readily soluble in water and solutions are more tolerant of salts and have a higher coagulation temperature.

8 Description

A white, yellowish-white or grayish-white powder or granules, hygroscopic after drying.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for hydroxyethylmethyl cellulose.

Test	PhEur 2005
Identification	+
Appearance of solution	+
pH	5.5–8.0
Apparent viscosity	+
Chlorides	⩽0.5%
Heavy metals	⩽20 ppm
Loss on drying	⩽10.0%
Sulfated ash	⩽1.0%

10 Typical Properties

Acidity/alkalinity: pH = 5.5–8.0 (2% w/v aqueous solution)
Moisture content: ⩽10%
Solubility: hydroxyethylmethyl cellulose is practically insoluble in hot water (above 60°C), acetone, ethanol (95%), ether, and toluene. It dissolves in cold water to form a colloidal solution.
Viscosity (dynamic): 22–30 mPa s (22–30 cP) for a 2% w/v aqueous solution at 20°C.

11 Stability and Storage Conditions

Hydroxyethylmethyl cellulose is hygroscopic and should therefore be stored under dry conditions away from heat.

12 Incompatibilities

—

13 Method of Manufacture

—

14 Safety

Hydroxyethylmethyl cellulose is used as an excipient in various oral and topical pharmaceutical preparations and is generally regarded as an essentially nontoxic and nonirritant material.

See Hypromellose for further information.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled. Eye protection and gloves are recommended.

16 Regulatory Status

GRAS listed. Included in nonparenteral medicines licensed in Europe (oral suspensions, tablets, and topical preparations).

17 Related Substances

Ethylcellulose; hydroxyethyl cellulose; hypromellose; methylcellulose.

18 Comments

—

19 Specific References

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20 General References

—

21 Authors

SC Owen, PJ Sheskey.

22 Date of Revision

2 August 2005.

Hydroxypropyl Cellulose

1 Nonproprietary Names

BP: Hydroxypropylcellulose
JP: Hydroxypropylcellulose
PhEur: Hydroxypropylcellulosum
USPNF: Hydroxypropyl cellulose

2 Synonyms

Cellulose, hydroxypropyl ether; E463; hyprolose; *Klucel*; *Methocel*; *Nisso HPC*; oxypropylated cellulose.

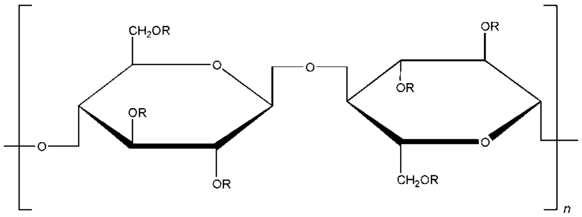
3 Chemical Name and CAS Registry Number

Cellulose, 2-hydroxypropyl ether [9004-64-2]

4 Empirical Formula and Molecular Weight

The PhEur 2005 and USPNF 23 describe hydroxypropyl cellulose as a partially substituted poly(hydroxypropyl) ether of cellulose. It may contain not more than 0.6% of silica or another suitable anticaking agent. Hydroxypropyl cellulose is commercially available in a number of different grades that have various solution viscosities. Molecular weight has a range of 50 000–1 250 000; *see also* Section 10.

5 Structural Formula



R is H or $[CH_2CH(CH_3)O]_mH$

6 Functional Category

Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations; *see* Table I.

In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder,(1) film-coating,(2) and extended-release-matrix former.(3–5) Concentrations of hydroxypropyl cellulose of 2–6% w/w may be used as a binder in either wet-granulation or dry, direct-compression tableting processes.(6–10) Concentrations of 15–35% w/w of hydroxypropyl cellulose may be used to produce tablets with an extended drug release.(11) The release rate of a drug increases with decreasing viscosity of hydroxypropyl cellulose. The addition of an anionic surfactant similarly increases the viscosity of hydroxypropyl cellulose and hence decreases the release rate of a drug. Typically, a 5% w/w solution of hydroxypropyl cellulose may be used to film-coat tablets. Aqueous solutions containing hydroxypropyl cellulose along with an amount of methyl cellulose or ethanolic solutions have been used.(12–14) Stearic acid or palmitic acid may be added to ethanolic hydroxypropyl cellulose solutions as plasticizers. Environmental concerns have limited the use of ethanol in film coating solutions. A low-substituted hydroxypropyl cellulose is used as a tablet disintegrant; see Hydroxypropyl Cellulose, Low-substituted.

Hydroxypropyl cellulose is also used in microencapsulation processes and as a thickening agent. In topical formulations, hydroxypropyl cellulose is used in transdermal patches and ophthalmic preparations.(15–17)

Hydroxypropyl cellulose is also used in cosmetics and in food products as an emulsifier and stabilizer.

Table I: Uses of hydroxypropyl cellulose.

Use	Concentration (%)
Extended release-matrix former	15–35
Tablet binder	2–6
Tablet film coating	5

8 Description

Hydroxypropyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder. *See also* Section 10.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for hydroxypropyl cellulose.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Apparent viscosity	+	+	+
Appearance of solution	+	+	—
pH (1 in 100)	5.0–7.5	5.0–8.5	5.0–8.0
Loss on drying	⩽5.0%	⩽7.0%	⩽5.0%
Residue on ignition	⩽0.5%	—	⩽0.2%
Sulfated ash	—	⩽1.6%	—
Arsenic	⩽2 ppm	—	—
Chlorides	+	⩽0.5%	—
Lead	—	—	⩽0.001%
Heavy metals	⩽20 ppm	⩽20 ppm	20 μg/g
Silica	—	⩽0.6%	—
Organic volatile impurities	—	—	+
Sulfate	⩽0.048%	—	—
Assay of hydroxypropoxy groups	53.4–77.5%	—	⩽80.5%

10 Typical Properties

Acidity/alkalinity: pH = 5.0–8.5 for a 1% w/v aqueous solution.

Density (bulk): ≈0.5 g/cm^3

Interfacial tension: 12.5 mN/m for a 0.1% w/v aqueous solution compared with mineral oil.

Melting point: softens at 130°C; chars at 260–275°C.

Moisture content: hydroxypropyl cellulose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air. Typical equilibrium moisture content values at 25°C are 4% w/w at 50% relative humidity and 12% w/w at 84% relative humidity. *See* Table III. *See also* Figure I.

Table III: Moisture content of *Klucel* (Aqualon).

Grade	Molecular weight	Moisture (%)
Klucel EF	≈80 000	0.59
Klucel LF	≈95 000	2.21
Klucel JF	≈140 000	1.44
Klucel GF	≈370 000	1.67
Klucel MF	≈850 000	1.52
Klucel HF	≈1 150 000	4.27

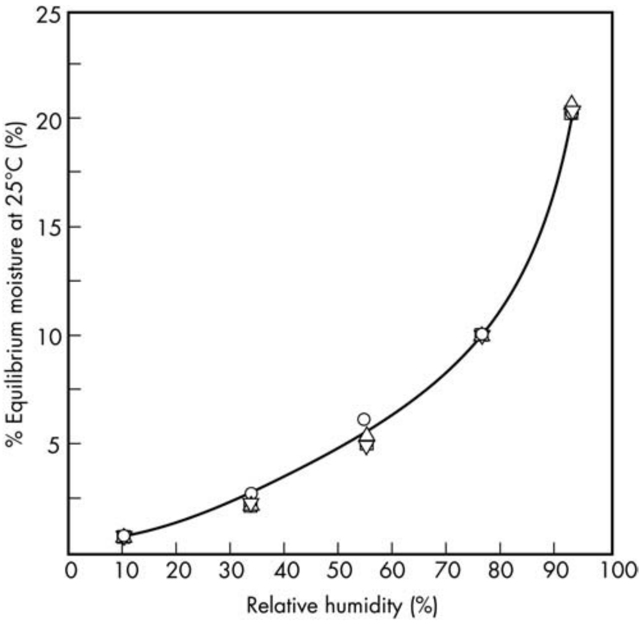


Figure 1: Equilibrium moisture content of various grades of hydroxypropyl cellulose.
○: *Klucel GF* (Aqualon, Lot #4996).
△: *Klucel JF* (Aqualon, Lot #4753).
▽: *Klucel LF* (Aqualon, Lot #4965).
□: *Klucel EF* (Aqualon, Lot #1223).

Particle size distribution:

Klucel (regular grind), 95% through a US #30 mesh (590 μm), and 99% through a US #20 mesh (840 μm);

Klucel (X-grind), 100% through a US #60 mesh (250 μm), and 80% through a US #100 mesh (149 μm).

Refractive index: n_D^{20} = 1.3353 for a 2% w/v aqueous solution.

Solubility: soluble 1 in 10 parts dichloromethane; 1 in 2.5 parts ethanol (95%); 1 in 2 parts methanol; 1 in 5 parts propan-2-ol; 1 in 5 parts propylene glycol; and 1 in 2 parts water. Practically insoluble in aliphatic hydrocarbons; aromatic hydrocarbons; carbon tetrachloride; petroleum distillates; glycerin; and oils.

Hydroxypropyl cellulose is freely soluble in water below 38°C, forming a smooth, clear, colloidal solution. In hot water, it is insoluble and is precipitated as a highly swollen floc at a temperature between 40 and 45°C. Hydroxypropyl cellulose is soluble in many cold or hot polar organic solvents such as dimethyl formamide; dimethyl sulfoxide; dioxane; ethanol (95%); methanol; propan-2-ol (95%); and propylene glycol. There is no tendency for precipitation in hot organic solvents. However, the grade of hydroxypropyl cellulose can have a marked effect upon solution quality in some organic liquids that are borderline solvents, such as acetone; butyl acetate; cyclohexanol; dichloromethane; lactic acid; methyl acetate; methyl ethyl ketone; propan-2-ol (99%); and *tert*-butanol. The higher-viscosity grades of hydroxypropyl cellulose tend to produce slightly inferior solutions. However, the solution quality in borderline solvents can often be greatly improved by the use of small quantities (5–15%) of a cosolvent. For example, dichloromethane is a borderline solvent for *Klucel HF* and solutions have a granular texture, but a smooth solution may be produced by adding 10% methanol.

Hydroxypropyl cellulose is compatible with a number of high-molecular-weight, high-boiling waxes and oils, and can be used to modify certain properties of these materials. Examples of materials that are good solvents for hydroxypropyl cellulose at an elevated temperature are acetylated monoglycerides, glycerides, pine oil, polyethylene glycol, and polypropylene glycol.

Specific gravity: 1.2224 for particles; 1.0064 for a 2% w/v aqueous solution at 20°C.

Surface tension: *see* Table IV.

Table IV: Surface tension (mN/m) of aqueous solutions of *Nisso HPC* (Nippon Soda Co. Ltd.) at 20°C.

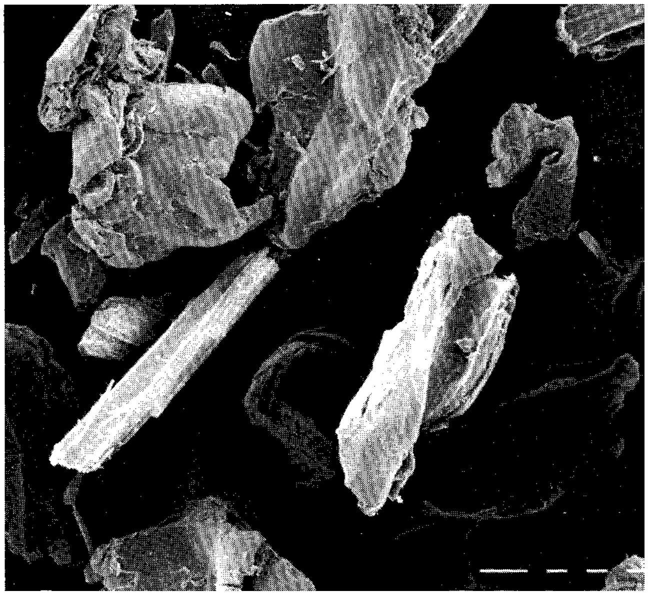
Grade	Surface tension (mN/m) at 20°C for aqueous solutions of stated concentration			
	0.01%	0.1%	1.0%	10.0%
Nisso HPC-L	51.0	49.1	46.3	45.8
Nisso HPC-M	54.8	49.7	46.3	—

Viscosity (dynamic): a wide range of viscosity types are commercially available; *see* Table V. Solutions should be prepared by gradually adding the hydroxypropyl cellulose to a vigorously stirred solvent. Increasing concentration produces solutions of increased viscosity. *See also* Section 11 for information on solution stability.

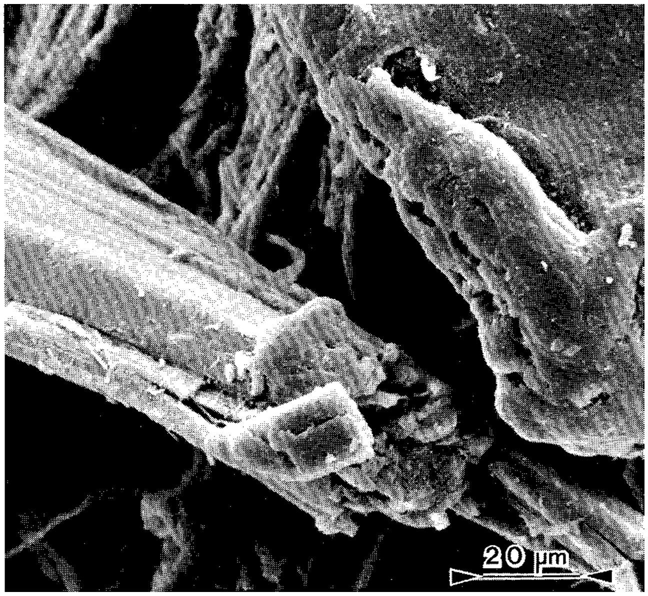
Table V: Viscosity of aqueous solutions of *Klucel* (Aqualon) at 25°C.

Grade	Viscosity (mPa s) of various aqueous solutions of stated concentration			
	1%	2%	5%	10%
Klucel HF	1500–3000	—	—	—
Klucel MF	—	4000–6500	—	—
Klucel GF	—	150–400	—	—
Klucel JF	—	—	150–400	—
Klucel LF	—	—	75–150	—
Klucel EF	—	—	—	200–600

SEM: 1
Excipient: Hydroxypropyl cellulose (*Klucel*)
Manufacturer: Aqualon
Magnification: 60×



SEM: 2
Excipient: Hydroxypropyl cellulose (*Klucel*)
Manufacturer: Aqualon
Magnification: 600×



11 Stability and Storage Conditions

Hydroxypropyl cellulose powder is a stable material, although it is hygroscopic after drying.

Aqueous solutions of hydroxypropyl cellulose are stable at pH 6.0–8.0, with the viscosity of solutions being relatively unaffected. However, at low pH aqueous solutions may undergo acid hydrolysis, resulting in chain scission and hence a decrease in solution viscosity. The rate of hydrolysis increases with increasing temperature and hydrogen ion concentration. At high pH, alkali-catalyzed oxidation may degrade the polymer and result in a decrease in viscosity of solutions. This degradation can occur owing to the presence of dissolved oxygen or oxidizing agents in a solution.

Increasing temperature causes the viscosity of aqueous solutions to decrease gradually until the viscosity drops suddenly at about 45°C owing to the limited solubility of hydroxypropyl cellulose. However, this process is reversible and on cooling the original viscosity is restored.

The high level of substitution of hydroxypropyl cellulose improves the resistance of the polymer to degradation by molds and bacteria.(14) However, aqueous solutions are susceptible to degradation under severe conditions and a viscosity decrease may occur. Certain enzymes produced by microbial action will degrade hydroxypropyl cellulose in solution.(18) Therefore, for prolonged storage, an antimicrobial preservative should be added to aqueous solutions. Solutions of hydroxypropyl cellulose in organic solvents do not generally require preservatives.

Ultraviolet light will also degrade hydroxypropyl cellulose and aqueous solutions may therefore decrease slightly in viscosity if exposed to light for several months.

Aqueous hydroxypropyl cellulose solutions have optimum stability when the pH is maintained at 6.0–8.0, and also when the solution is protected from light, heat, and the action of microorganisms.

Hydroxypropyl cellulose powder should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Hydroxypropyl cellulose in solution demonstrates some incompatibility with substituted phenol derivatives, such as methylparaben and propylparaben. The presence of anionic polymers may increase the viscosity of hydroxypropyl cellulose solutions.

The compatibility of hydroxypropyl cellulose with inorganic salts varies depending upon the salt and its concentration; *see* Table VI. Hydroxypropyl cellulose may not tolerate high concentrations of other dissolved materials.

The balance of the hydrophilic–lipophilic properties of the polymer, which are required for dual solubility, reduces its ability to hydrate with water and it therefore tends to be salted out in the presence of high concentrations of other dissolved materials.

The precipitation temperature of hydroxypropyl cellulose is lower in the presence of relatively high concentrations of other dissolved materials that compete for the water in the system; *see* Table VII.

13 Method of Manufacture

A purified form of cellulose is reacted with sodium hydroxide to produce a swollen alkali cellulose that is chemically more reactive than untreated cellulose. The alkali cellulose is then reacted with propylene oxide at elevated temperature and pressure. The propylene oxide can be substituted on the cellulose through an ether linkage at the three reactive hydroxyls present on each anhydroglucose monomer unit of the cellulose chain. Etherification takes place in such a way that hydroxypropyl substituent groups contain almost entirely secondary hydroxyls. The secondary hydroxyl present in the side chain is available for further reaction with the propylene oxide, and 'chaining-out' may take place. This results in the

Table VI: Compatibility of hydroxypropyl cellulose (*Nisso HPC*) with inorganic salts in aqueous solutions.[(a)]

Salt	Concentration of salt (% w/w)						
	2	3	5	7	10	30	50
Aluminum sulfate	S	S	I	I	I	I	I
Ammonium nitrate	S	S	S	S	S	I	I
Ammonium sulfate	S	S	I	I	I	I	I
Calcium chloride	S	S	S	S	S	T	I
Dichromic acid	S	S	S	S	S	S	S
Disodium hydrogenphosphate	S	S	I	I	I	I	I
Ferric chloride	S	S	S	S	S	I	I
Potassium ferrocyanide	S	S	S	I	I	I	I
Silver nitrate	S	S	S	S	S	S	T
Sodium acetate	S	S	S	S	I	I	I
Sodium carbonate	S	S	I	I	I	I	I
Sodium chloride	S	S	S	S	I	I	I
Sodium nitrate	S	S	S	S	S	I	I
Sodium sulfate	S	S	I	I	I	I	I
Sodium sulfite	S	S	I	I	I	I	I
Sodium thiosulfate	T	T	T	I	I	I	I

[(a)] S, completely soluble; T, turbid white; I, insoluble.

Table VII: Variation in precipitation temperature of hydroxypropyl cellulose (*Klucel H*) in the presence of other materials.

Ingredients and concentrations	Precipitation temperature (°C)
1% *Klucel H*	41
1% *Klucel H* + 1.0% sodium chloride	38
1% *Klucel H* + 5.0% sodium chloride	30
0.5% *Klucel H* + 10% sucrose	41
0.5% *Klucel H* + 30% sucrose	32
0.5% *Klucel H* + 40% sucrose	20
0.5% *Klucel H* + 50% sucrose	7

formation of side chains containing more than 1 mole of combined propylene oxide.

14 Safety

Hydroxypropyl cellulose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

Hydroxypropyl cellulose is generally regarded as an essentially nontoxic and nonirritant material.(19,20) However, the use of hydroxypropyl cellulose as a solid ocular insert has been associated with rare reports of discomfort or irritation, including hypersensitivity and edema of the eyelids. Adverse reactions to hydroxypropyl cellulose are rare. However, it has been reported that a single patient developed contact dermatitis due to hydroxypropyl cellulose in a transdermal estradiol patch.(21)

The WHO has not specified an acceptable daily intake for hydroxypropyl cellulose since the levels consumed were not considered to represent a hazard to health.(22) Excessive consumption of hydroxypropyl cellulose may, however, have a laxative effect.

LD_{50} (rat, IV): 0.25 g/kg(23)
LD_{50} (rat, oral): 10.2 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hydroxypropyl cellulose dust may be irritant to the eyes; eye protection is recommended. Excessive dust generation should be avoided to minimize the risk of explosions.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets; topical and transdermal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Hydroxyethyl cellulose; hydroxypropyl cellulose, low-substituted; hypromellose.

18 Comments

Hydroxypropyl cellulose is a thermoplastic polymer that can be processed by virtually all fabrication methods used for plastics.

It is also used in hot-melt extruded films for topical use. When it is produced with chlorpheniramine maleate, the matrix is stabilized, allowing film processing at lower temperatures.(24) Mucoadhesive hydroxypropyl cellulose microspheres have been prepared for powder inhalation preparations.(25) A specification for hydroxypropyl cellulose is included in the Food Chemicals Codex (FCC).

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RJ Harwood.

22 Date of Revision

17 August 2005.

Hydroxypropyl Cellulose, Low-substituted

1 Nonproprietary Names

JP: Low-substituted hydroxypropylcellulose
USPNF: Low-substituted hydroxypropyl cellulose

2 Synonyms

Hyprolose, low-substituted; *L-HPC*.

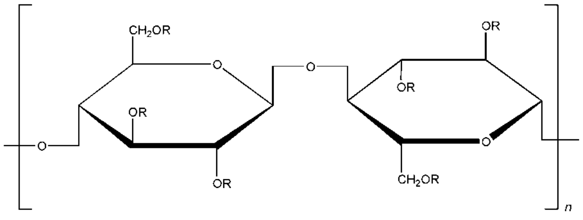
3 Chemical Name and CAS Registry Number

Cellulose, 2-hydroxypropyl ether (low-substituted) [78214-41-2]

4 Empirical Formula and Molecular Weight

The USPNF 23 describes low-substituted hydroxypropyl cellulose as a low-substituted hydroxypropyl ether of cellulose. When dried at 105°C for 1 hour, it contains not less than 5.0% and not more than 16.0% of hydroxypropoxy groups (—$OCH_2CHOHCH_3$). Low-substituted hydroxypropyl cellulose is commercially available in a number of different grades that have different particle sizes and substitution levels.

5 Structural Formula



R is H or $[CH_2CH(CH_3)O]_mH$

6 Functional Category

Tablet and capsule disintegrant; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Low-substituted hydroxypropyl cellulose is widely used in oral solid-dosage forms. It is primarily used in tableting as a disintegrant, and as a binder in wet granulation. It has been used in the preparation of rapidly disintegrating tablets produced by direct compression methods.(1,2) In addition, low-substituted hydroxypropyl cellulose has been used to delay the release of drug from a tablet matrix.(3)

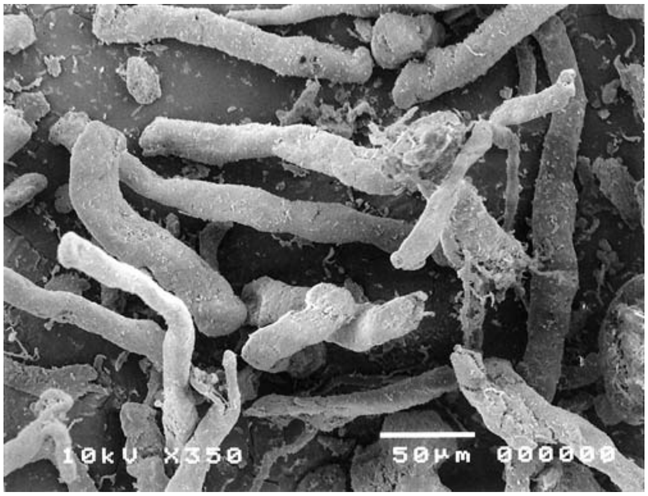
There are a number of grades that have different particle sizes and substitution levels. *LH-11* has the medium substitution level and the largest particle size, and is typically used as an anticapping agent and disintegrant for direct compression. *LH-21* is used as a binder and disintegrant for tablets through the wet-granulation process. *LH-31* is a small-particle grade used especially for extrusion to produce granules, as it has a small particle size that is better for passing a screen. Lower substitution grades *LH-22* and *LH-32* can be used when high binding strength is not necessary. If higher binding strength is needed, higher substitution grades *LH-20* and *LH-30* are also available.

The typical content of low-substituted hydroxypropyl cellulose in a formulation is approximately 5–25%.

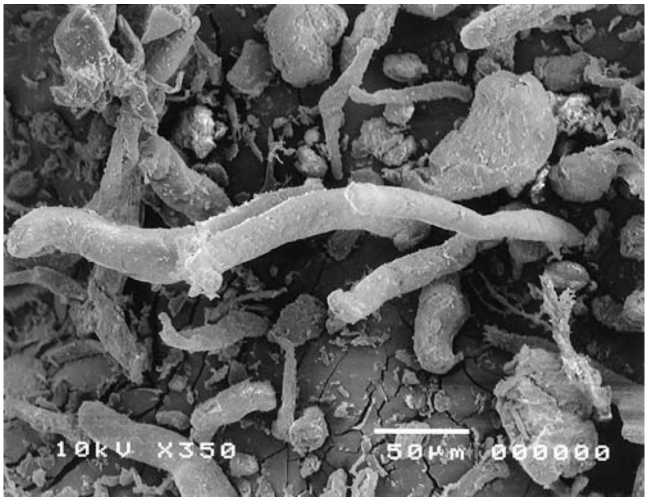
8 Description

Low-substituted hydroxypropyl cellulose occurs as a white to yellowish white powder or granules. It is odorless or has a slight, characteristic odor, and it is tasteless.

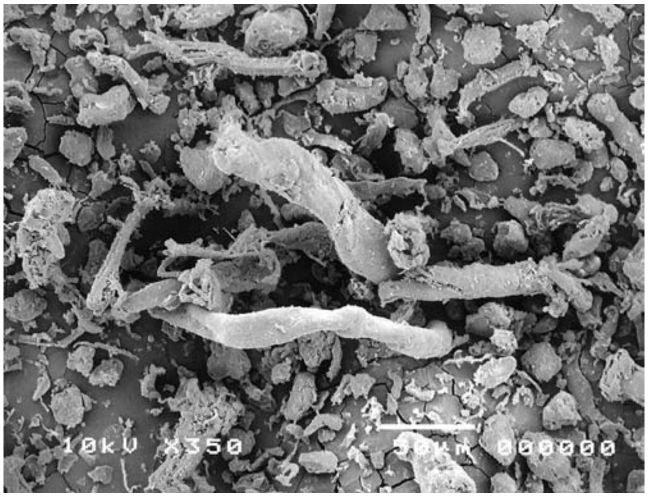
SEM: 1
Excipient: Low-substituted hydroxypropyl cellulose, type *LH-11*
Manufacturer: Shin-Etsu
Magnification: 350×



SEM: 2
Excipient: Low-substituted hydroxypropyl cellulose, type *LH-21*
Manufacturer: Shin-Etsu
Magnification: 350×



SEM: 3
Excipient: Low-substituted hydroxypropyl cellulose, type *LH-31*
Manufacturer: Shin-Etsu
Magnification: 350×



9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for hydroxypropyl cellulose, low substituted.

Test	JP 2001	USPNF 23
Identification	+	+
Chloride	⩽0.335%	⩽0.36%
Heavy metals	⩽10 ppm	⩽0.001%
Arsenic	⩽2 ppm	—
pH	5.0–7.5	—
Loss on drying	⩽6.0%	⩽5.0%
Residue on ignition	⩽1.0%	⩽0.5%
Assay (of hydroxypropoxy groups)	5.0–16.0%	5.0–16.0%

10 Typical Properties

Acidity/alkalinity: pH = 5.0–7.5 for 1% w/v aqueous suspension.
Angle of repose: *see* Table II.
Ash: 0.3–0.4%
Density (bulk): *see* Table II.
Density (tapped): *see* Table II.
Melting point: decomposition at 275°C.
Moisture content:
8% at 33% relative humidity;
38% at 95% relative humidity.
Specific gravity: 1.46
Solubility: practically insoluble in ethanol (95%) and in ether. Dissolves in a solution of sodium hydroxide (1 in 10) and produces a viscous solution. Insoluble, but swells in water.

11 Stability and Storage Conditions

Low-substituted hydroxypropyl cellulose is a stable, though hygroscopic, material. The powder should be stored in a well-closed container.

Table II: Typical properties of hydroxypropyl cellulose, low-substituted, for selected grades.

Grade	Hydroxy-propoxy content (%)	Angle of repose (°)	Average particle size (μm)	Density (bulk) (g/cm^3)	Density (tapped) (g/cm^3)
LH-11	11	49	50	0.32	0.56
LH-21	11	45	40	0.36	0.62
LH-31	11	49	25	0.28	0.59
LH-22	8	48	40	0.36	0.62
LH-32	8	53	25	0.28	0.59
LH-20	13	48	40	0.36	0.62
LH-30	13	51	25	0.28	0.59

12 Incompatibilities

Alkaline substances may interact. If a tablet formulation contains such a material, its disintegration may be extended after storage.

13 Method of Manufacture

Low-substituted hydroxypropyl cellulose is manufactured by reacting alkaline cellulose with propylene oxide at elevated temperature. Following the reaction, the product is recrystallized by neutralization, washed, and milled.

14 Safety

Low-substituted hydroxypropyl cellulose is generally regarded as a nontoxic and nonirritant material.

Animal toxicity studies showed no adverse effects in rats fed orally 6 g/kg/day over 6 months. No teratogenic effects were noted in rabbits and rats fed 5 g/kg/day.(4–7)

LD$_{50}$ (rat, oral): 15 g/kg(4)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Excessive dust generation should be avoided to minimize the risk of explosions.

16 Regulatory Status

Approved for use in pharmaceuticals in Europe, Japan, USA, and other countries. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Hydroxypropyl cellulose.

18 Comments

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19 Specific References

1 Kawashima Y, Takeuchi H, Hino T, *et al.* Low-substituted hydroxypropylcellulose as a sustained-drug release matrix base or disintegrant depending on its particle size and loading in formulation. *Pharm Res* 1993; **10**(3): 351–355.
2 Ishikawa T, Mukai B, Shiaishi S, *et al.* Preparation of rapidly disintegrating tablet using new types of microcrystalline cellulose (PH-M series) and low-substituted hydroxypropylcellulose or

spherical sugar granules by direct compression method. *Chem Pharm Bull* 2001; **49**(2): 134–139.

3 Jeko ZB, Sipos T, Kertai EH, Mezey G. Comparison of dissolution-rate curves of carbamazepine from different hydrophilic matrix tablets. *Acta Pharm* 1999; **49**: 267–273.

4 Kitagawa H, Yano H, Saito H, Fukuka Y. Acute, subacute and chronic toxicities of hydroxypropylcellulose of low-substitution in rats. *Pharmacometrics* 1976; **12**: 41–66.

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6 Kitagawa H, Satoh T, Saito H, *et al*. Teratological study of hydroxypropylcellulose of low substitution (L-HPC) in rabbits. *Pharmacometrics* 1978; **16**: 259–269.

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Shin-Etsu Chemical Co. Ltd. Technical literature: *L-HPC, low-substituted hydroxypropyl cellulose*, 1991.

Shin-Etsu Chemical Co. Ltd. Technical literature: *L-HPC, NF Disintegrant-binder*, 2000.

21 Authors

RJ Harwood.

22 Date of Revision

17 August 2005.

Hydroxypropyl Starch

1 Nonproprietary Names

None adopted.

2 Synonyms

E1440; hydroxylpropyl starch.

3 Chemical Name and CAS Registry Number

Hydroxypropyl starch [113894-92-1]

4 Empirical Formula and Molecular Weight

Hydroxypropyl starch is a derivative of natural starch; it is described in the JPE 2004 as a hydroxypropyl ether of corn starch.

5 Structural Formula

See Section 4.

6 Functional Category

Binder; disintegrant; emulsifying agent; thickening agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Hydroxypropyl starch is a modified starch and has been used in combination with carrageenan in the production of soft capsules.(1,2) Hydroxypropyl starch has been used experimentally in hydrophilic matrices, where it was shown to be an effective matrix for tablets designed for controlled-release drug delivery systems.(3) It has also been used experimentally in the production of hydrophilic matrices by direct compression.(4)

It is used in antiseptics and is used widely in cosmetics. It is also used analytically as a bioseparation aqueous-phase-forming polymer.(5)

8 Description

Hydroxypropyl starch occurs as a free-flowing white to off-white coarse powder.

9 Pharmacopeial Specifications

See Section 18.

10 Typical Properties

Acidity/alkalinity: pH = 4.5–7.0 (10% w/v aqueous dispersion).

Solubility: practically insoluble in water, ethanol (95%), and ether.

11 Stability and Storage Conditions

Hydroxypropyl starch is stable at high humidity and is considered to be inert under normal conditions. It is stable in emulsion systems at pH 3–9.

12 Incompatibilities

See Section 18.

13 Method of Manufacture

Hydroxypropyl starch is produced industrially from natural starch, using propylene oxide as the modifying reagent in the presence of alkali, adding hydroxypropyl ($CH(OH)CH_2CH_3$) groups at the OH positions by an ether linkage.

14 Safety

Hydroxypropyl starch is widely used in cosmetics and food products. It is also used in oral pharmaceutical formulations. The WHO has set an acceptable daily intake for hydroxypropyl starch at 'not limited' since it was well tolerated on oral consumption.(6)

LD_{50} (rat, oral): 0.218 g/kg(7)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe.

17 Related Substances

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18 Comments

Hydroxypropyl starch–methyl methacrylate (HS-MMA) has been used experimentally in hydrophilic matrices produced by direct compression.(4) Pregelatinized hydroxypropyl starch has been shown to exhibit good disintegrating properties, and can be used as a binder in wet granulation.(8)

Although it is not currently included in the pharmacopeias, a specification for hydroxypropyl starch is included in the Japanese Pharmaceutical Excipients (JPE) 2004; *see* Table I.(9)

Hydroxypropyl starch is compatible with cationic ingredients (monovalent, divalent), oils, emollients, and silicone.

The EINECS number for hydroxypropyl starch is 232-679-6.

Table I: JPE 2004 specification for hydroxypropyl starch.

Test	JPE 2004
Description	+
Identification	+
pH	5.0–7.5
Chloride	⩽0.142%
Heavy metals	⩽20 ppm
Arsenic	⩽5 ppm
Loss on drying	⩽15.0%
Residue on ignition	⩽0.5%
Content of hydroxypropyl group after drying	2.0–7.0%

19 Specific References

1 Draper PR, Tanner KE, Getz JJ, et al. Film forming compositions comprising modified starches and iota-carrageenan and methods for manufacturing soft capsules using the same. International Patent WO 013677; 1999.
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20 General References

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21 Authors

D Thassu, SA Shah.

22 Date of Revision

15 August 2005.

Hypromellose

1 Nonproprietary Names

BP: Hypromellose
JP: Hydroxypropylmethylcellulose
PhEur: Hypromellosum
USP: Hypromellose

2 Synonyms

Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; *Methocel*; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; *Metolose*; *Tylopur*.

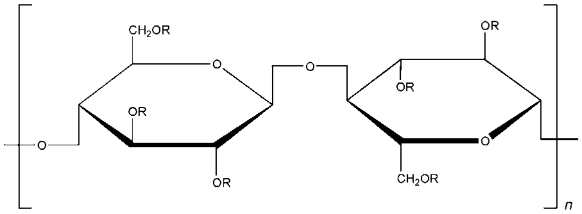
3 Chemical Name and CAS Registry Number

Cellulose hydroxypropyl methyl ether [9004-65-3]

4 Empirical Formula and Molecular Weight

The PhEur 2005 describes hypromellose as a partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20°C. Hypromellose defined in the USP 28 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g., hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group ($OCH_2CH(OH)CH_3$), calculated on a dried basis. It contains methoxy and hydroxypropoxy groups conforming to the limits for the types of hypromellose stated in Table I. Molecular weight is approximately 10 000–1 500 000. The JP 2001 includes three separate monographs for hypromellose: hydroxypropylmethylcellulose 2208, 2906, and 2910, respectively.

5 Structural Formula



where R is H, CH_3, or $CH_3CH(OH)CH_2$

6 Functional Category

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations.

In oral products, hypromellose is primarily used as a tablet binder,(1) in film-coating,(2–7) and as a matrix for use in extended-release tablet formulations.(8–12) Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules.

Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. Examples of film-coating materials that are commercially available include *AnyCoat C*, *Spectracel*, and *Pharmacoat*.

Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

8 Description

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder. *See also* Section 10.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acidity/alkalinity: pH = 5.5–8.0 for a 1% w/w aqueous solution.

Ash: 1.5–3.0%, depending upon the grade and viscosity.

Autoignition temperature: 360°C

Density (bulk): 0.341 g/cm^3

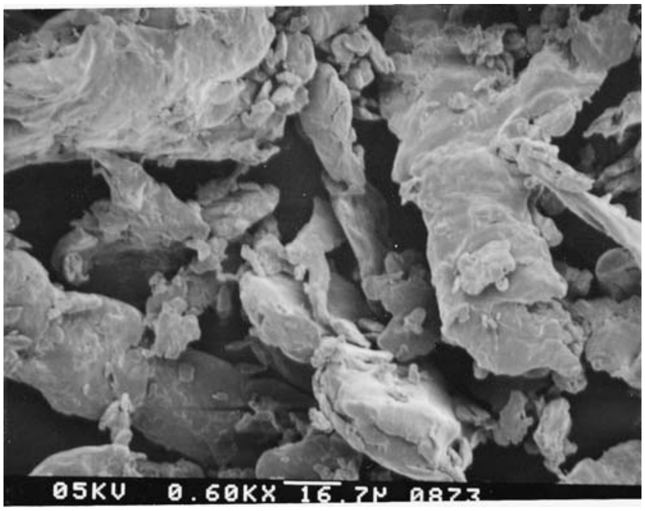
Density (tapped): 0.557 g/cm^3

Density (true): 1.326 g/cm^3

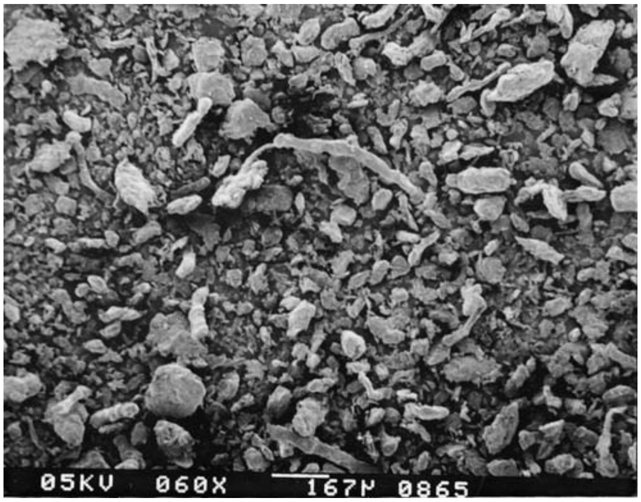
Melting point: browns at 190–200°C; chars at 225–230°C. Glass transition temperature is 170–180°C.

Moisture content: hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air. *See* Figure 1.

SEM: 1
Excipient: Hypromellose
Manufacturer: Dow Chemical Co.
Lot No.: ME20012N11
Magnification: 600×
Voltage: 5 kV



SEM: 2
Excipient: Hypromellose
Manufacturer: Dow Chemical Co.
Lot No.: ME20012N11
Magnification: 60×
Voltage: 5 kV



Solubility: soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents. *See also* Section 11.

Specific gravity: 1.26

Table I: Pharmacopeial specifications for hypromellose.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	—	+	—
Appearance of solution	+	+	—
pH (1% w/w solution)	5.0–8.0	5.5–8.0	—
Apparent viscosity	+	+	+
Loss on drying	⩽5.0%	⩽10.0%	⩽5.0%
Residue on ignition	⩽1.5%	—	—
For viscosity grade >50 mPa s	—	—	⩽1.5%
For viscosity grade ⩽50 mPa s	—	—	⩽3.0%
For type 1828 of all viscosities	—	—	⩽5.0%
Sulfated ash	—	⩽1.0%	—
Chlorides	⩽0.284%	⩽0.5%	—
Heavy metals	⩽10 ppm	⩽20 ppm	⩽0.001%
Iron	⩽100 ppm	—	—
Arsenic	⩽2 ppm	—	—
Organic volatile impurities	—	—	+
Methoxy content			
Type 1828	—	—	16.5–20.0%
Type 2208	19.0–24.0%	—	19.0–24.0%
Type 2906	27.0–30.0%	—	27.0–30.0%
Type 2910	28.0–30.0%	—	28.0–30.0%
Hydroxypropoxy content			
Type 1828	—	—	23.0–32.0%
Type 2208	4.0–12.0%	—	4.0–12.0%
Type 2906	4.0–7.5%	—	4.0–7.5%
Type 2910	7.0–12.0%	—	7.0–12.0%

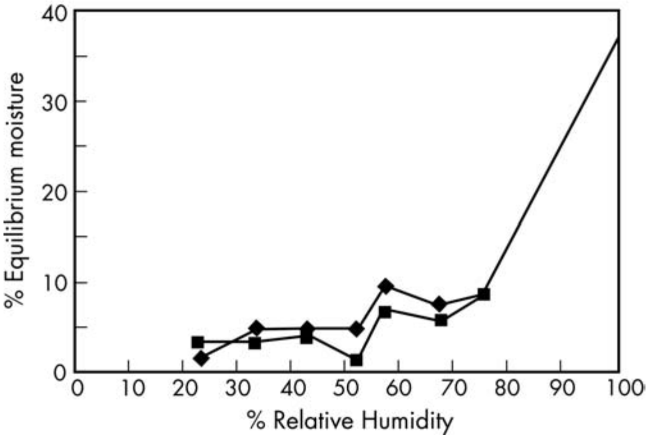


Figure 1: Absorption–desorption isotherm for hypromellose.
◆: Sorption
■: Desorption

Viscosity (dynamic): a wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous hypromellose solutions. Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions; *see* Table II.

Table II: Typical viscosity values for 2% (w/v) aqueous solutions of *Methocel* (Dow Chemical Co.). Viscosities measured at 20°C.

Methocel product	USP 28 designation	Nominal viscosity (mPa s)
Methocel K100 Premium LVEP	2208	100
Methocel K4M Premium	2208	4000
Methocel K15M Premium	2208	15 000
Methocel K100M Premium	2208	100 000
Methocel E4M Premium	2910	4000
Methocel F50 Premium	2906	50
Methocel E10M Premium CR	2906	10 000
Methocel E3 Premium LV	2906	3
Methocel E5 Premium LV	2906	5
Methocel E6 Premium LV	2906	6
Methocel E15 Premium LV	2906	15
Methocel E50 Premium LV	2906	50
Metolose 60SH	2910	50, 4000, 10 000
Metolose 65SH	2906	50, 400, 1500, 4000
Metolose 90SH	2208	100, 400, 4000, 15 000

To prepare an aqueous solution, it is recommended that hypromellose is dispersed and thoroughly hydrated in about 20–30% of the required amount of water. The water should be vigorously stirred and heated to 80–90°C, then the remaining hypromellose should be added. Sufficient cold water should then be added to produce the required volume.

When a water-miscible organic solvent such as ethanol (95%), glycol, or mixtures of ethanol and dichloromethane are used, the hypromellose should first be dispersed into the organic solvent, at a ratio of 5–8 parts of solvent to 1 part of hypromellose. Cold water is then added to produce the required volume.

11 Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying.

Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gel point is 50–90°C, depending upon the grade and concentration of material.

Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage.(13) However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative: when hypromellose is used as a viscosity-increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking.

Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

12 Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

13 Method of Manufacture

A purified form of cellulose, obtained from cotton linters or wood pulp, is reacted with sodium hydroxide solution to produce a swollen alkali cellulose that is chemically more reactive than untreated cellulose. The alkali cellulose is then treated with chloromethane and propylene oxide to produce methyl hydroxypropyl ethers of cellulose. The fibrous reaction product is then purified and ground to a fine, uniform powder or granules.

14 Safety

Hypromellose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

Hypromellose is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may have a laxative effect.(14) The WHO has not specified an acceptable daily intake for hypromellose since the levels consumed were not considered to represent a hazard to health.(15)

LD_{50} (mouse, IP): 5 g/kg(16)
LD_{50} (rat, IP): 5.2 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hypromellose dust may be irritant to the eyes and eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combustible.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (ophthalmic preparations; oral capsules, suspensions, syrups, and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Hydroxyethyl cellulose; hydroxyethylmethyl cellulose; hydroxypropyl cellulose; hypromellose phthalate; methylcellulose.

18 Comments

Powdered or granular, surface-treated grades of hypromellose are also available that are dispersible in cold water. These are not recommended for oral use. A specification for hypromellose is contained in the Food Chemicals Codex (FCC).

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21 Authors

RJ Harwood.

22 Date of Revision

17 August 2005.

Hypromellose Acetate Succinate

1 Nonproprietary Names

USPNF: Hypromellose acetate succinate

2 Synonyms

Aqoat; *Aqoat AS-HF/HG*; *Aqoat AS-LF/LG*; *Aqoat AS-MF/MG*; cellulose, 2-hydroxypropyl methyl ether, acetate succinate; HPMCAS.

3 Chemical Name and CAS Registry Number

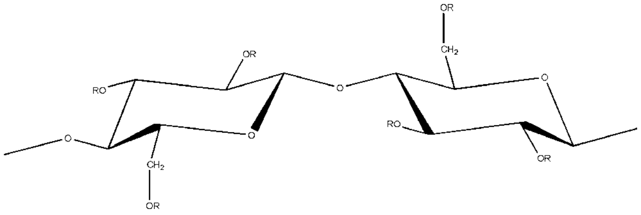
Cellulose, 2-hydroxypropylmethyl ether, acetate hydrogen butanedioate [71138-97-1]

4 Empirical Formula and Molecular Weight

Hypromellose acetate succinate is a mixture of acetic acid and monosuccinic acid esters of hydroxypropylmethyl cellulose.(1–4) It is available in several grades, which vary in extent of substitution, mainly of acetyl and succinoyl groups, and in particle size (fine or granular). When dried at 105°C for one hour, it contains 12.0–28.0% of methoxy groups; 4.0–23.0% of hydroxypropoxy groups; 2.0–16.0% of acetyl groups; and 4.0–28.0% of succinoyl groups.

The molecular weight of hypromellose acetate succinate is approximately 55 000–93 000 Daltons, measured by gel permeation chromatography using polyethylene oxide as a relative reference standard.

5 Structural Formula



Where -OR represents one of the following functional groups -hydroxyl, methoxyl, 2-hydroxypropoxyl, acetyl, or succinoyl.

6 Functional Category

Component of controlled-release or sustained-release dosage forms; enteric coating agent; film-forming agent; solid dispersion vehicle.

7 Applications in Pharmaceutical Formulation or Technology

Hypromellose acetate succinate is commonly used in oral pharmaceutical formulations as a film coating, as well as enteric coating material for tablets or granules.(5–7) It is insoluble in gastric fluid but will swell and dissolve rapidly in the upper intestine. For aqueous film-coating purposes, a dispersion of hypromellose acetate succinate fine powder and triethyl citrate (as a plasticizer) in water is commonly utilized.(4,8,9) Organic solvents can also be used as vehicles for applying this polymer as a film coating.

Hypromellose acetate succinate may be used alone or in combination with other soluble or insoluble binders in the preparation of granules with sustained drug-release properties; the release rate is pH-dependent.

Dispersions of poorly soluble drugs with hypromellose acetate succinate are prepared using techniques such as mechanical grinding, solvent evaporation, and melt extrusion.(10–14)

8 Description

Hypromellose acetate succinate is a white to off-white powder or granules.(4) It has a faint acetic acid-like odor and a barely detectable taste. Hypromellose acetate succinate is available in several grades, according to the pH at which the polymer dissolves (low, L; medium, M; and high, H) and its predominant particle size (cohesive fine powder, F; or free-flowing granules, G).

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for hypromellose acetate succinate.

Test	USPNF 23 (Suppl. 2)
Identification	+
Viscosity	+
Loss on drying	⩽0.5.0%
Residue on ignition	⩽0.20%
Heavy metals	⩽0.001%
Limit of free acetic and succinic acids	+
Content of acetyl and succinyl groups	+
Content of methoxy and 2–hydroxypropoxy groups	+

10 Typical Properties

Density (bulk):
0.2–0.3 g/cm^3 for *Aqoat MF* (Shin Etsu);
0.2–0.5 g/cm^3 for *Aqoat MG* (Shin Etsu).
Density (tapped):
0.3–0.5 g/cm^3 for *Aqoat MF* (Shin Etsu);
0.3–0.6 g/cm^3 for *Aqoat MG* (Shin Etsu).
Density (true): 1.27–1.29 g/cm^3(4)
Equilibrium moisture content: 2–3% w/w at ambient temperature and humidity (≈25°C, 40% RH).(4) *See also* Figure 1.
Glass transition temperature: 113 ±2°C (differential scanning calorimetry; dried sample)
Particle size distribution: 10% < 1 μm; 50% < 5 μm; 90% < 10 μm for *Aqoat MF* (Shin Etsu).

10% < 200 μm; 50% < 800 μm; 90% < 1000 μm for *Aqoat MG* (Shin Etsu).

Solubility: practically insoluble in ethanol (95%), hexane, unbuffered water, and xylene. On the addition of acetone, or a mixture of ethanol (95%) and dichloromethane (1 : 1), a clear or turbid viscous liquid is produced. Hypromellose acetate succinate can be dissolved in buffers of pH greater than 4.5 with the rank order of solubility for the various grades (*see* Section 8) increasing with the ratio of acetyl over succinoyl substitution. The exact pH value at which the polymer dissolves depends on the buffer type and ionic strength, although the rank order for the different grades is independent of the buffer used.

Viscosity (dynamic): *see* Figure 2.

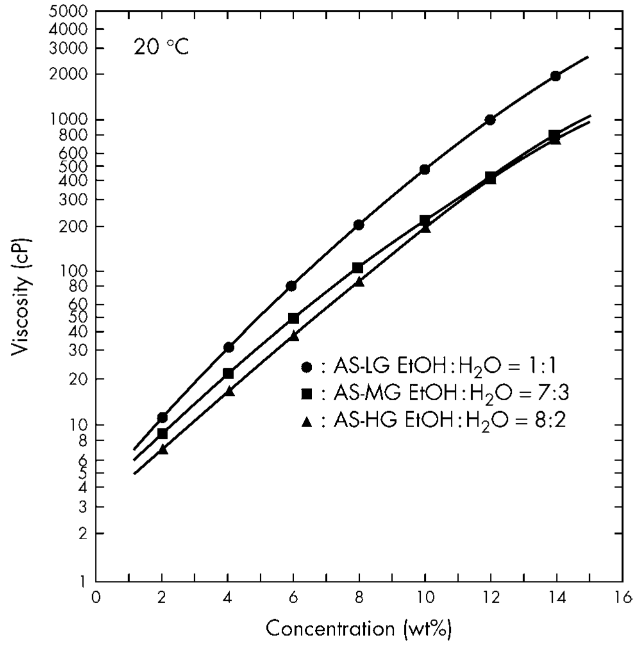


Figure 1: Viscosity of different grades of *Aqoat* (Shin-Etsu).[4]

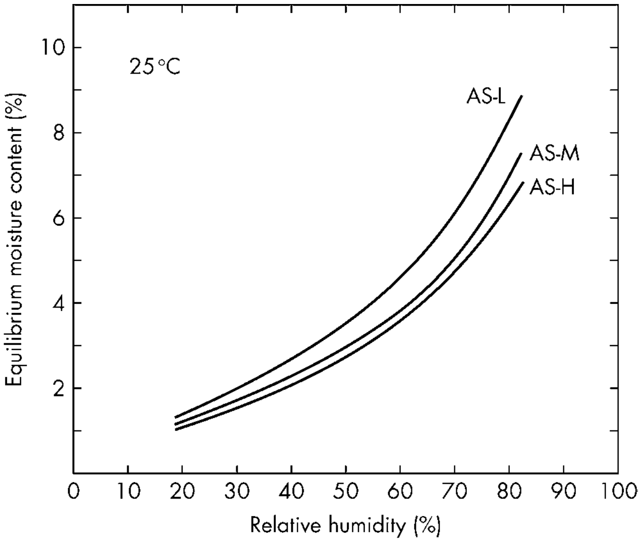
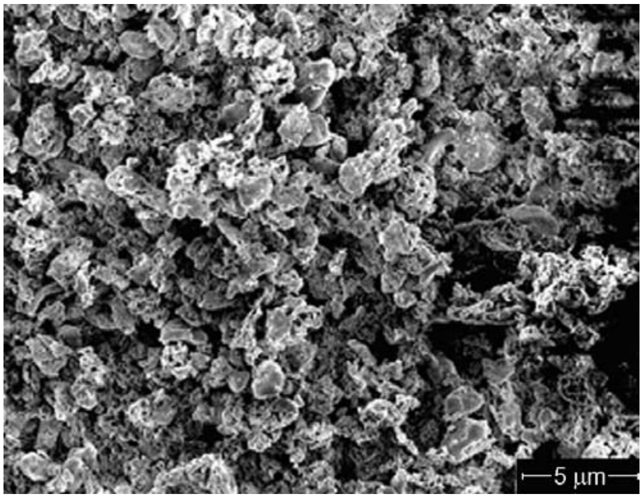
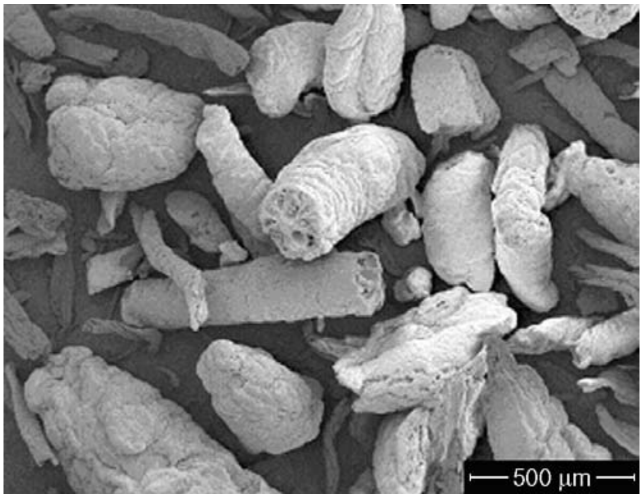


Figure 2: Equilibrium moisture content of *Aqoat* (Shin-Etsu) at different relative humidities.[4]

SEM: 1
Excipient: Aqoat MF
Manufacturer: Shin Etsu
Magnification: 1000×



SEM: 2
Excipient: Aqoat MG
Manufacturer: Shin Etsu
Magnification: 50×



11 Stability and Storage Conditions

Hypromellose acetate succinate should be stored in a well-closed container, in a cool, dry place. In such storage conditions, hypromellose acetate succinate is a stable material. It is stable for four years after manufacturing.[4] Hypromellose acetate succinate is hygroscopic. It is hydrolyzed to acetic acid and succinic acid, and the hypromellose polymer starts to form if dissolved in 1 mol/L sodium hydroxide for more than two hours.[15] The hydrolysis is the main degradation pathway that is responsible for increasing amounts of free acids in storage, especially upon exposure to moisture.

12 Incompatibilities

Hypromellose acetate succinate is incompatible with strong acids or bases, oxidizing agents, and sustained levels of elevated humidity.

13 Method of Manufacture

Hypromellose acetate succinate is produced by the esterification of hypromellose with acetic anhydride and succinic anhydride, in a reaction medium of a carboxylic acid, such as acetic acid, and using an alkali carboxylate, such as sodium acetate, as catalyst.(16) The fibrous reaction product is precipitated out by adding a large volume of water to the reaction medium. Purification is achieved by thorough washing with water. The granular grade of hypromellose acetate succinate that is so obtained can be pulverized to a fine powder if required.

14 Safety

The safety and pharmacological profiles of hypromellose acetate succinate are similar to those of other ether and ester derivatives of cellulose.(17–21) All nonclinical studies reported in the literature identify no target organs for toxicity by hypromellose acetate succinate.(22,23) It has also been reported that hypromellose acetate succinate does not alter fertility in rats, does not produce any developmental anomalies in rats and rabbits, and does not alter perinatal and postnatal development in rats when assessed up to 2500 mg/kg.(24–27)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hypromellose acetate succinate dust may be irritant to the eyes. Excessive dust generation should be avoided to minimize the risks of explosions. Avoid contact with open flame, heat, or sparks. Avoid contact with acids, peroxides, and other oxidizing materials. Eye protection is recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide for use in oral preparations (capsules, and delayed-action preparations). Hypromellose acetate succinate has been approved for use in commercial pharmaceutical products in the USA and in Japan.

17 Related Substances

Carboxymethyl cellulose; cellulose acetate; cellulose acetate phthalate; cellulose, microcrystalline; ethylcellulose; hypromellose; hypromellose phthalate; hydroxyethyl cellulose; hydroxypropyl cellulose; methylcellulose.

18 Comments

A specification for hypromellose acetate succinate is also included in the Japanese Pharmaceutical Excipients (JPE); *see* Table II.

Table II: JPE specification for hypromellose acetate succinate.

Test	**JPE 1998(1,2)**		
	LG, LF	**MG, MF**	**HG, HF**
Appearance	Conforms	Conforms	Conforms
Identification	Conforms	Conforms	Conforms
Viscosity (mm^2/s)	2.4–3.6	2.4–3.6	2.4–3.6
Heavy metals (%w/w)	$\leqslant$0.001	$\leqslant$0.001	$\leqslant$0.001
Arsenic (%w/w)	$\leqslant$0.0002	$\leqslant$0.0002	$\leqslant$0.0002
Free succinic acid (%)[a]	$\leqslant$1.0	$\leqslant$1.0	$\leqslant$1.0
Loss on drying (%)	$\leqslant$5.0	$\leqslant$5.0	$\leqslant$5.0
Residue on ignition (%)	$\leqslant$0.20	$\leqslant$0.20	$\leqslant$0.20
Methoxyl content (%)	20.0–24.0	21.0–25.0	22.0–26.0
Hydroxypropoxyl content (%)	5.0–9.0	5.0–9.0	6.0–10.0
Acetyl content (%)	5.0–9.0	7.0–11.0	10.0–14.0
Succinoyl content (%)	14.0–18.0	10.0–14.0	4.0–8.0

[a] The titration method in JPE is only capable of monitoring the total free acid amount, which is here termed free succinic acid. It has been demonstrated that the total free acids consists of free acetic and succinic acids.(15)

A new accurate and robust analytical method based on liquid chromatography has been developed for the analysis of free organic acids, and acetyl and succinoyl substitutions in hypromellose acetate succinate.(15) It provides efficient separation and sensitive quantitation of free acetic and succinic acids. Another new analytical method based on liquid chromatography has also been developed for the analysis of methoxyl and 2-hydroxypropoxyl substitutions in hypromellose acetate succinate.(28)

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21 Authors

R Chen, BC Hancock, RM Shanker.

22 Date of Revision

24 August 2005.

Hypromellose Phthalate

1 Nonproprietary Names

BP: Hypromellose phthalate
JP: Hydroxypropylmethylcellulose phthalate
PhEur: Hypromellosi phthalas
USPNF: Hypromellose phthalate

2 Synonyms

Cellulose phthalate hydroxypropyl methyl ether; HPMCP; hydroxypropyl methylcellulose benzene-1,2-dicarboxylate; 2-hydroxypropyl methylcellulose phthalate; methylhydroxypropylcellulose phthalate.

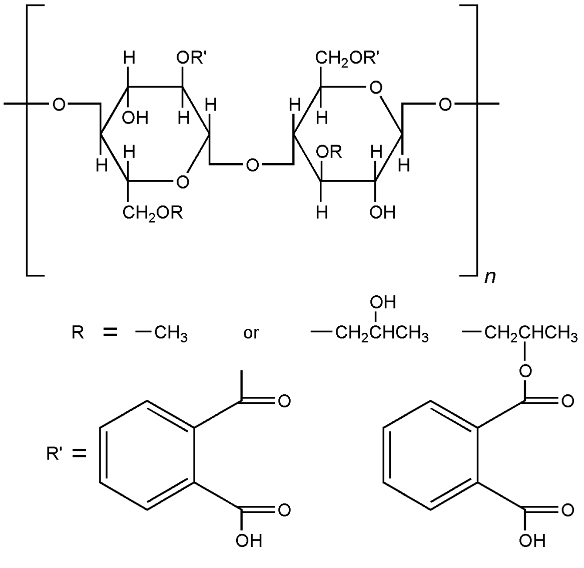
3 Chemical Name and CAS Registry Number

Cellulose, hydrogen 1,2-benzenedicarboxylate, 2-hydroxypropyl methyl ether [9050-31-1]

4 Empirical Formula and Molecular Weight

Hypromellose phthalate is a cellulose in which some of the hydroxyl groups are replaced with methyl ethers, 2-hydroxypropyl ethers, or phthalyl esters. Several different types of hypromellose phthalate are commercially available with molecular weights in the range 20 000–200 000. Typical average values are 80 000–130 000.(1)

5 Structural Formula



6 Functional Category

Coating agent.

7 Applications in Pharmaceutical Formulation or Technology

Hypromellose phthalate is widely used in oral pharmaceutical formulations as an enteric coating material for tablets or granules.(2–8) Hypromellose phthalate is insoluble in gastric fluid but will swell and dissolve rapidly in the upper intestine. Generally, concentrations of 5–10% of hypromellose phthalate are employed with the material being dissolved in either a dichloromethane : ethanol (50 : 50) or an ethanol : water (80 : 20) solvent mixture. Hypromellose phthalate can normally be applied to tablets and granules without the addition of a plasticizer or other film formers, using established coating techniques. However, the addition of a small amount of plasticizer or water can avoid film cracking problems; many commonly used plasticizers, such as diacetin, triacetin, diethyl and dibutyl phthalate, castor oil, acetyl monoglyceride, and polyethylene glycols, are compatible with hypromellose phthalate. Tablets coated with hypromellose phthalate disintegrate more rapidly than tablets coated with cellulose acetate phthalate.

Hypromellose phthalate can be applied to tablet surfaces using a dispersion of the micronized hypromellose phthalate powder in an aqueous dispersion of a suitable plasticizer such as triacetin, triethyl citrate, or diethyl tartrate along with a wetting agent.(9)

Hypromellose phthalate may be used alone or in combination with other soluble or insoluble binders in the preparation of granules with sustained drug-release properties; the release rate is pH-dependent. Since hypromellose phthalate is tasteless and insoluble in saliva, it can also be used as a coating to mask the unpleasant taste of some tablet formulations. Hypromellose phthalate has also been co-precipitated with a poorly soluble drug to improve dissolution characteristics.(10)

8 Description

Hypromellose phthalate occurs as white to slightly off-white, free-flowing flakes or as a granular powder. It is odorless or with a slightly acidic odor and has a barely detectable taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for hypromellose phthalate.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Water	⩽5.0%	⩽5.0%	⩽5.0%
Viscosity (20°C)	+	—	+
Residue on ignition	⩽0.20%	⩽0.20%	⩽0.20%
Chloride	⩽0.07%	⩽0.07%	⩽0.07%
Heavy metals	⩽10 ppm	⩽10 ppm	⩽0.001%
Free phthalic acid	⩽1.0%	⩽1.0%	⩽1.0%
Organic volatile impurities	—	—	+
Phthalyl content	—	21.0–35.0%	21.0–35.0%
Type 200731	27.0–35.0%	—	—
Type 220824	21.0–27.0%	—	—

10 Typical Properties

Angle of repose:
37° for *HP-50*;
39° for *HP-55*;
38° for *HP-55S*.(11)

Density:
1.82 g/cm^3 for *HP-50*;
1.65 g/cm^3 for *HP-55*.(11)

Density (bulk):
0.278 g/cm^3 for *HP-50*;
0.275 g/cm^3 for *HP-55*;
0.239 g/cm^3 for *HP-55S*.(11)

Density (tapped):
0.343 g/cm^3 for *HP-50*;
0.306 g/cm^3 for *HP-55*;
0.288 g/cm^3 for *HP-55S*.(11)

Melting point: 150°C. Glass transition temperature is 137°C for *HP-50* and 133°C for *HP-55*.(12)

Moisture content: hypromellose phthalate is hygroscopic; it takes up 2–5% of moisture at ambient temperature and humidity conditions. For the moisture sorption isotherm of *HP-50* measured at 25°C, *see* Figure 1.

Particle size distribution: *see* Figure 2.

Solubility: readily soluble in a mixture of acetone and methyl or ethyl alcohol (1 : 1), in a mixture of methyl alcohol and dichloromethane (1 : 1), and in aqueous alkali. Practically insoluble in water and dehydrated alcohol and very slightly soluble in acetone. The solubilities of the *HP-50* and *HP-55* grades, in various solvents and solvent mixtures, are shown in Table II.(11)

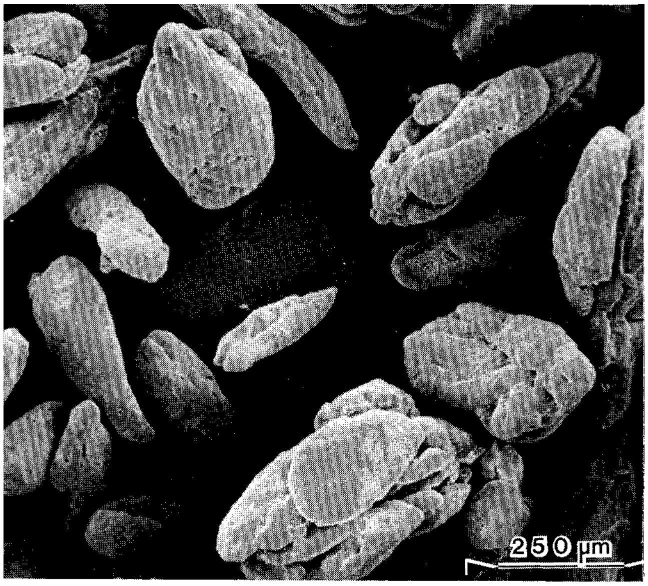
Viscosity: *see* Figures 3 and 4.

Table II: Solubility of hypromellose phthalate (*HP-50* and *HP-55*, Shin-Etsu Chemical Co. Ltd.).

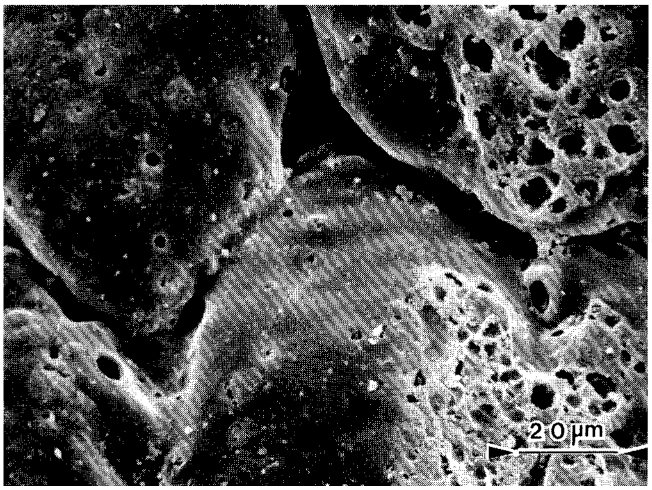
Solvent	**Solubility**	
HP-50	***HP-55***	
Acetone	S/I	S
Acetone : dichloromethane	S/I	S
Acetone : ethanol	S/S	S
Acetone : methanol	S	S
Acetone : 2-propanol	S/S	S
Acetone : water (95 : 5)	S	S
Benzene : methanol	S	S
Dichloromethane	S/I	S/I
Dichloromethane : ethanol	S	S
Dichloromethane : methanol	S	S
Dichloromethane : 2-propanol	S/S	S
Dioxane	S	S
Ethanol (95%)	S/I	S/I
Ethyl acetate	X	S/I
Ethyl acetate : ethanol	S/S	S
Ethyl acetate : methanol	S	S
Ethyl acetate : 2-propanol	S/I	S
Methanol	S/I	S/I
Methyl ethyl ketone	S/I	S
Propan-2-ol	X	S/I

Note: solubilities are for the pure solvent, or a (1 : 1) solvent mixture, unless otherwise indicated.
S = soluble, clear solution.
S/S = slightly soluble, cloudy solution.
S/I = swells but insoluble.
X = insoluble.

SEM: 1
Excipient: Hypromellose phthalate (*HP-55*)
Manufacturer: Shin-Etsu Chemical Co. Ltd.
Magnification: 60×



SEM: 2
Excipient: Hypromellose phthalate (*HP-55*)
Manufacturer: Shin-Etsu Chemical Co. Ltd.
Magnification: 600×



11 Stability and Storage Conditions

Hypromellose phthalate is chemically and physically stable at ambient temperature for at least 3–4 years and for 2–3 months at 40°C and 75% relative humidity.(11) It is stable on exposure to UV light for up to 3 months at 25°C and 70% relative humidity. Drums stored in a cool, dry place should be brought to room temperature before opening to prevent condensation of moisture on inside surfaces. After 10 days at 60°C and 100% relative humidity, 8–9% of carbyoxybenzoyl group were hydrolyzed. In general, hypromellose phthalate is more stable than cellulose acetate phthalate. At ambient storage conditions, hypromellose phthalate is not susceptible to microbial attack.

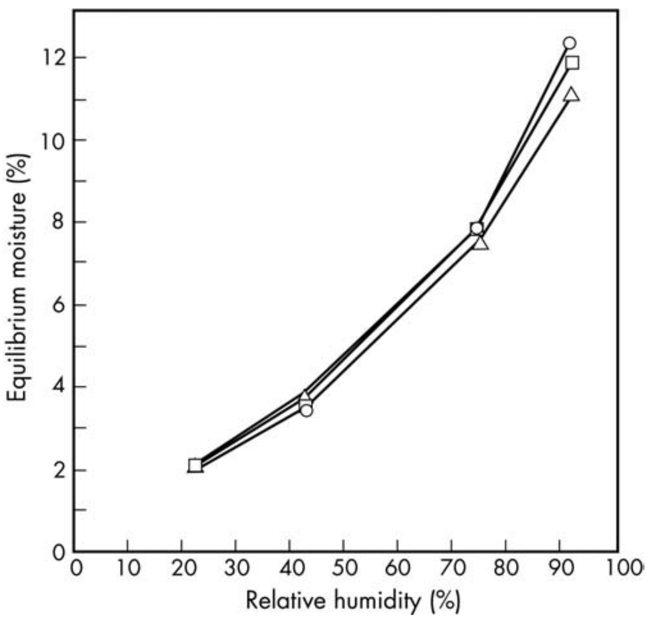


Figure 1: Equilibrium moisture content of hypromellose phthalate (Shin-Etsu Chemical Co. Ltd.) at 25°C.(11)
○: *HP-50*
□: *HP-55*
△: *HP-55S*

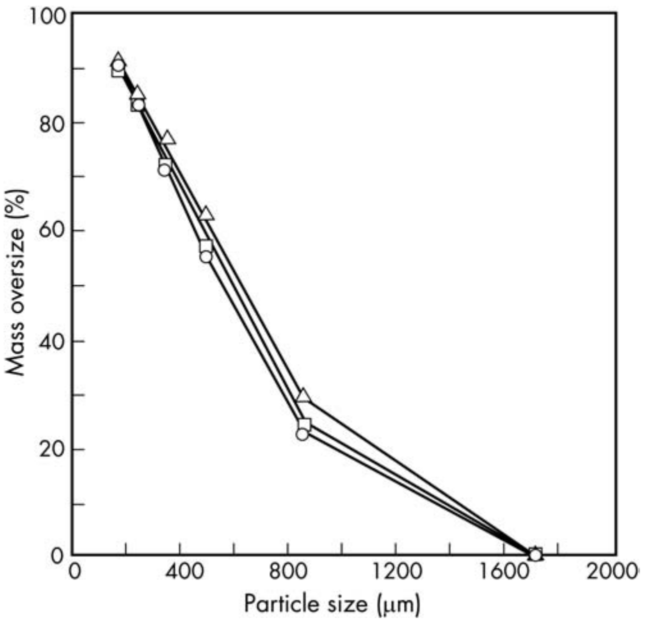


Figure 2: Particle size distribution of hypromellose phthalate (Shin-Etsu Chemical Co. Ltd).(11)
○: *HP-50*
□: *HP-55*
△: *HP-55S*

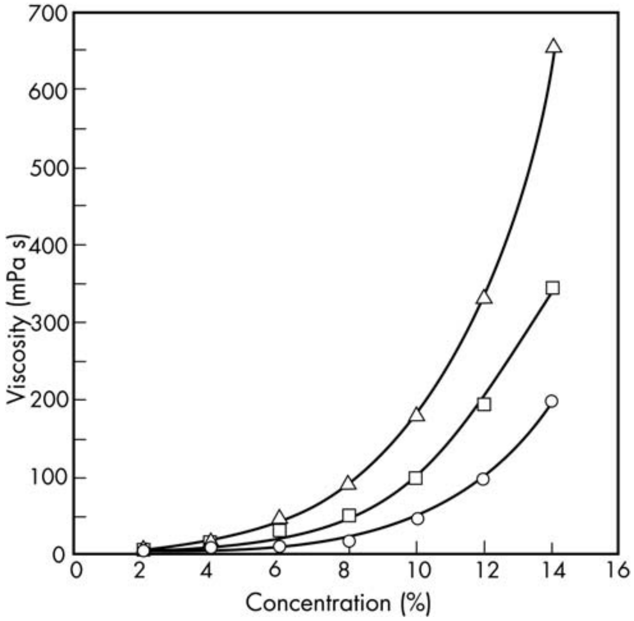


Figure 3: Dynamic viscosity of hypromellose phthalate (*HP-50*) (Shin-Etsu Chemical Co. Ltd.) in various solvent mixtures at 20°C.(11)
○: Acetone : ethanol (1 : 1)
□: Dichloromethane : ethanol (1 : 1)
△: Ethanol : water (1 : 1)

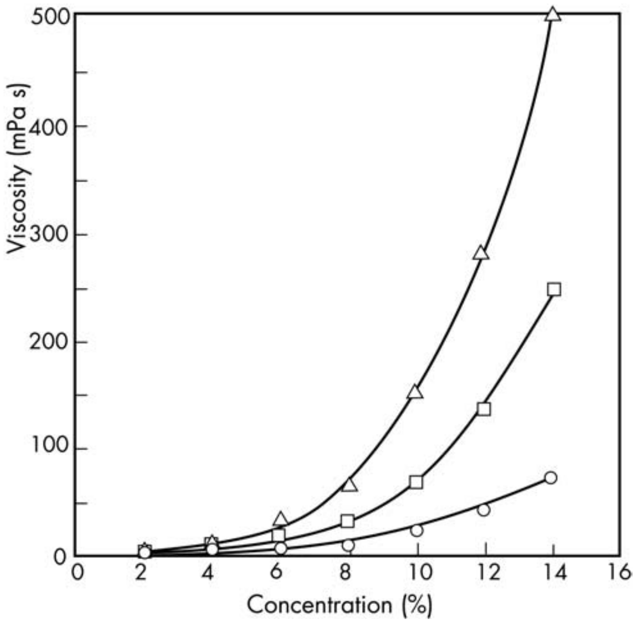


Figure 4: Dynamic viscosity of hypromellose phthalate (*HP-55*) (Shin-Etsu Chemical Co. Ltd.) in various solvent mixtures at 20°C.(11)
○: Acetone : ethanol (1 : 1)
□: Dichloromethane : ethanol (1 : 1)
△: Ethanol : water (8 : 2)

12 Incompatibilities

Incompatible with strong oxidizing agents.

Splitting of film coatings has been reported rarely, most notably with coated tablets that contain microcrystalline cellulose and calcium carboxymethylcellulose. Film splitting has also occurred when a mixture of acetone : propan-2-ol or dichloromethane : propan-2-ol has been used as the coating solvent, or when coatings have been applied in conditions of low temperature and humidity. However, film splitting may be avoided by careful selection of formulation composition, including solvent, by use of a higher molecular weight grade of polymer, or by suitable selection of plasticizer.

The addition of more than about 10% titanium dioxide to a coating solution of hypromellose phthalate, which is used to produce a colored film coating, may result in coating with decreased elasticity and resistance to gastric fluid.(11)

13 Method of Manufacture

Hypromellose phthalate is prepared by the esterification of hypromellose with phthalic anhydride. The degree of alkyloxy and carboxybenzoyl substitution determines the properties of the polymer and in particular the pH at which it dissolves in aqueous media.

14 Safety

Hypromellose phthalate is widely used, primarily as an enteric coating agent, in oral pharmaceutical formulations. Chronic and acute animal feeding studies on several different species have shown no evidence of teratogenicity or toxicity associated with hypromellose phthalate.(13–17) Hypromellose phthalate is generally regarded as a nonirritant and nontoxic material.

LD_{50} (rat, oral): >15 g/kg(13)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Although no threshold limit value has been set for hypromellose phthalate, it should be handled in a well-ventilated environment and the generation of dust should be minimized.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Cellulose acetate phthalate; hypromellose.

18 Comments

Various grades of hypromellose phthalate are available with differing degrees of substitution and physical properties, e.g., grades *HP-50*, *HP-55*, and *HP-55S* (Shin-Etsu Chemical Co Ltd). *See* Table III.

The number following ‘HP’ in each grade designation refers to the pH value (×10) at which the polymer dissolves in aqueous buffer solutions. The designation ‘S’ in *HP-55S* indicates a higher molecular weight grade, which produces films with a greater resistance to cracking.

Table III: Types of hypromellose phthalate available from Shin-Etsu Chemical Co. Ltd.

Property	Grade of hypromellose phthalate		
	HP-50	***HP-55***	***HP-55S***
Substitution type	220824	200731	200731
Hydroxypropoxy content	6–10%	5–9%	5–9%
Methoxy content	20–24%	18–22%	18–22%
Phthalyl content	21–27%	27–35%	27–35%
Molecular weight	84 000	78 000	132 000

In the USA, the substitution type is indicated by a six digit number: the first two digits represent the approximate percentage content of methoxy groups; the next two digits represent the approximate percentage content of hydroxypropoxy groups; and the final two digits represent the approximate percentage content of phthalyl groups.

To dissolve hypromellose phthalate in acetone : ethanol (95%) or dichloromethane : alcohol solvent systems, the hypromellose phthalate should first be well dispersed in alcohol before adding acetone or dichloromethane. When using acetone : dichloromethane, hypromellose phthalate should be first dispersed in the dichloromethane and then the acetone added to the system. A specification for hypromellose phthalate is contained in the Food Chemicals Codex (FCC).

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21 Authors

SR Goskonda, JC Lee.

22 Date of Revision

15 August 2005.

Imidurea

1 Nonproprietary Names

USPNF: Imidurea

2 Synonyms

Biopure 100; *Germall 115*; imidazolidinyl urea; methanebis[*N*,*N*′ (5-ureido-2,4-diketotetrahydroimidazole)-*N*,*N*-dimethylol]; 1,1′-methylenebis{3-[3-(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl]urea}; *Tri-Stat IU*.

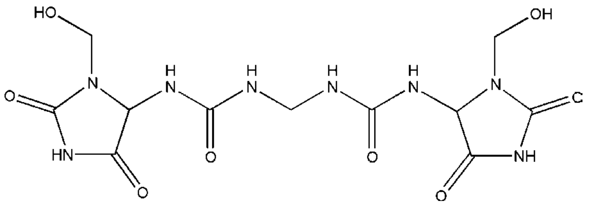
3 Chemical Name and CAS Registry Number

N, *N*″-Methylenebis{*N*′-[3-(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl]urea} [39236-46-9]

4 Empirical Formula and Molecular Weight

$C_{11}H_{16}N_8O_8$	388.29 (for anhydrous)
$C_{11}H_{16}N_8O_8.H_2O$	406.33 (for monohydrate)

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

Imidurea is a broad-spectrum antimicrobial preservative used in cosmetics and topical pharmaceutical formulations; typical concentrations used are 0.03–0.5% w/w. It is effective between pH 3–9 and is reported to have synergistic effects when used with parabens; *see* Section 10.

8 Description

Imidurea is a white, free-flowing odorless powder.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for imidurea.

Test	USPNF 23
Identification	+
Color and clarity of solution	+
pH (1% w/v solution)	6.0–7.5
Loss on drying	⩽3.0%
Residue on ignition	⩽3.0%
Heavy metals	⩽0.001%
Organic volatile impurities	+
Nitrogen content (dried basis)	26.0–28.0%

10 Typical Properties

Acidity/alkalinity: pH = 6.0–7.5 (1% w/v aqueous solution).

Antimicrobial activity: predominantly an antibacterial preservative, imidurea also has some selective antifungal properties. Used at concentrations between 0.03–0.5% w/w it is effective between pH 3–9, although preservative efficacy is best seen in slightly acidic solutions. Synergistic effects have been reported and preservative activity is considerably enhanced, particularly against fungi, when used in combination with parabens.(1,2) A cosmetic formulation containing 0.5% imidurea, 0.2% methylparaben, and 0.1% propylparaben was effectively preserved against various *Pseudomonas* species.(3) For reported minimum inhibitory concentrations (MICs), *see* Table II.(4)

Table II: Minimum inhibitory concentrations (MICs) for imidurea.

Microorganism	MIC (μg/mL)
Aspergillus niger	8000
Candida albicans	8000
Escherichia coli	2000
Klebsiella pneumoniae	2000
Penicillium notatum	8000
Pseudomonas aeruginosa	2000
Pseudomonas cepacia	2000
Pseudomonas fluorescens	2000
Staphylococcus aureus	1000

Solubility: soluble in water and in glycerol, but insoluble in almost all organic solvents.(4) *See also* Table III.

11 Stability and Storage Conditions

Imidurea is hygroscopic and should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Imidurea is compatible with other preservatives including sorbic acid and quaternary ammonium compounds.(5) It is also compatible with other pharmaceutical and cosmetic excipients including proteins, nonionic surfactants, and lecithin.(6)

Table III: Solubility of imidurea.

Solvent	Solubility at 20°C
Ethanol	Very slightly soluble
Ethanol (90%)	Very slightly soluble
Ethanol (70%)	1 in 330
Ethanol (60%)	1 in 25
Ethanol (50%)	1 in 2.5
Ethanol (30%)	1 in 0.8
Ethylene glycol[a]	1 in 0.7
Glycerin[a]	1 in 1
Methanol	Very slightly soluble
Mineral oil	Practically insoluble
Propan-2-ol	Practically insoluble
Propylene glycol[a]	1 in 0.8
Sesame oil	Very slightly soluble
Water	1 in 0.5

[a] Slow to dissolve and requires heating and stirring.

13 Method of Manufacture

Imidurea is commercially prepared by a complex synthetic route.

14 Safety

Imidurea is widely used in cosmetics and topical pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material.(5) However, there have been some reports of contact dermatitis associated with imidurea, although these are relatively few considering its widespread use in cosmetics.(7–10)

Although imidurea releases formaldehyde, it does not appear to be associated with cross-sensitization with formaldehyde or other formaldehyde-releasing compounds.

LD_{50} (mouse, oral): 7.2 g/kg(11,12)
LD_{50} (rabbit, skin): > 8 g/kg
LD_{50} (rat, oral): 11.3 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Imidurea may be irritant to the eyes. Eye protection and gloves are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (topical preparations). Accepted for use in cosmetics in Europe and the USA. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Diazolidinyl urea.

Diazolidinyl urea

Empirical formula: $C_8H_{14}N_4O_7$
Molecular weight: 278.23
CAS number: [78491-02-8]
Synonyms: *Germall II*; *N*-(hydroxymethyl)-*N*-(1,3-dihydroxymethyl-2,5-dioxo-4-imidazolidinyl)-*N*′-(hydroxymethyl) urea.
Appearance: white, free-flowing hygroscopic powder, with a faint characteristic odor.
Antimicrobial activity: similar to imidurea.(13,14) Diazolidinyl urea is the most active of the imidazolidinyl family of preservatives. Used in concentrations of 0.1–0.5% w/w, at pH 3–9, it has predominantly antibacterial properties. Typical MICs are: *Aspergillus niger* 4000 μg/mL; *Candida albicans* 8000 μg/mL; *Escherichia coli* 1000 μg/mL; *Pseudomonas aeruginosa* 1000 μg/mL; *Staphylococcus aureus* 250 μg/mL.
Solubility: very soluble in water.
Safety:
LD_{50} (mouse, oral): 3.7 g/kg(15)
LD_{50} (rat, oral): 2.6 g/kg
Comments: the EINECS number for diazolidinyl urea is 278-928-2.

18 Comments

Imidurea is the best known of a family of heterocyclic urea derivatives that are effective antimicrobial preservatives. Diazolidinyl urea has the greatest antimicrobial activity.

The EINECS number for imidurea is 254-372-6.

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21 Authors

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22 Date of Revision

25 August 2005.

Inulin

1 Nonproprietary Names

BP: Inulin
USPNF: Inulin

2 Synonyms

Beneo; *Frutafit*; oligofructose; polyfructose; *Raftiline*.

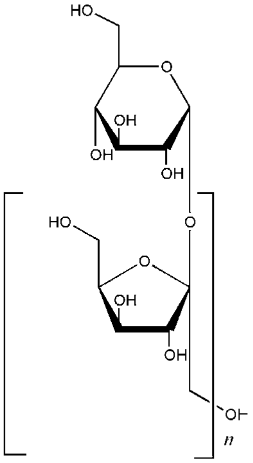
3 Chemical Name and CAS Registry Number

Inulin [9005-80-5]

4 Empirical Formula and Molecular Weight

$C_6H_{11}O_4(C_6H_{11}O_4)_nOH$ ≈5000

5 Structural Formula



Inulin is a naturally occurring polysaccharide consisting of a linear chain of linked D-fructose molecules, having one terminal glucose molecule.

6 Functional Category

Diagnostic aid; sweetening agent; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Inulin has many potential uses in pharmaceutical applications, as a filler–binder in tablet formulations;(1) to stabilize therapeutic proteins;(2) or to enhance the dissolution of lipophilic drugs.(3) Methacrylated inulin hydrogels have been investigated for the development of colon-specific drug delivery systems.(4)

Inulin is used as a diagnostic agent to measure the glomerular filtration rate.(5) It is used in the food industry as a sweetener and stabilizer; and also as a pro-biotic, where it has been shown to provide protection against inflammatory and malignant colonic diseases in animals.(6,7) It is also used as a noncaloric dietary fiber supplement.

8 Description

Inulin occurs as an odorless white powder with a neutral to slightly sweet taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for inulin.

Test	BP 2004	USPNF 23
Identification	+	+
Acidity	+	4.5–7.0
Clarity and color of solution	+	+
Microbial limit	—	⩽1000/g
Loss on drying	⩽10.0%	⩽10.0%
Specific rotation	–36.5° to –40.5°	–32.0° to –40.0°
Residue on ignition	⩽0.1%	⩽0.05%
Sulfate	⩽200 ppm	⩽0.05%
Calcium	⩽270 ppm	⩽0.5%
Chloride	⩽170 ppm	⩽0.014%
Heavy metals	—	⩽5 ppm
Arsenic	⩽1 ppm	—
Lead	⩽2 ppm	—
Oxalate	+	—
Glucose and fructose	+	+
Assay (dried basis)	—	94.0–102.0%

10 Typical Properties

Acidity/alkalinity: pH = 4.5–7.0 (10% w/v aqueous solution)
Density: 1.35 g/cm^3
Hygroscopicity: hygroscopic in moist air.
Melting point: 178°C
Solubility: soluble in hot water and solutions of dilute acids and alkalis; slightly soluble in cold water and organic solvents.
Specific gravity: 1.35

11 Stability and Storage Conditions

Inulin is slightly hygroscopic and should be stored at cool to normal temperatures, in air-tight and water-tight containers.

12 Incompatibilities

Inulin is incompatible with strong oxidizing agents.

13 Method of Manufacture

Inulin is extracted from the tubers of *Dahlia variabilis*, Helianthus, in a procedure similar to the extraction of sugar from sugar beet.

14 Safety

Inulin is a naturally occurring plant polysaccharide and is one of the major constituents of the Compositae family. Inulin is recommended to diabetics, as it has a mild sweet taste, but is not absorbed and does not affect blood sugar levels. It is used widely in the food industry as a sweetener and stabilizer.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Inulin may cause mild irritation to the skin and the eyes. Eye protection and gloves are recommended.

16 Regulatory Status

GRAS listed.

17 Related Substances

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18 Comments

Hollow spheres of inulin have been found to have both brittle and ductile properties. On compression, these spheres will undergo fragmentation followed by plastic deformation, resulting in better compressibility over solid inulin spheres. In its amorphous state, inulin has a high glass transition temperature, slow crystallization, and low hygroscopicity. As a binder in solid dosage forms, inulin can increase the dissolution rate of drugs such as diazepam and can enhance the stability of other lipophilic drug molecules.(3,8) Experimentally, methacrylated inulin hydrogels have been synthesized specifically for colon targeting.(9,10)

Inulin is used as a diagnostic agent to measure the glomerular filtration rate. It has also entered the food supplement market as a prebiotic and as a noncaloric dietary fiber supplement. Radio-labelled forms of inulin are available as radiochemicals for research.

19 Specific References

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20 General References

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21 Authors

JT Irwin.

22 Date of Revision

24 August 2005.

Iron Oxides

1 Nonproprietary Names

None adopted.

2 Synonyms

(a) Iron oxide black: *Bayferrox 306*; black magnetic oxide; black oxide, precipitated; black rouge; CI 77499; E172; ethiops iron; ferric ferrous oxide; ferrosoferric oxide; iron oxide; iron (II, III) oxide; iron (III) oxide; iron (II) oxide, black; iron oxides (Fe_3O_4); magnetite; pigment black 11; triiron tetraoxide.
(b) Iron (III) oxide hydrated: *Bayferrox 920Z*; CI 77492; E172; ferric hydroxide; ferric hydroxide oxide; ferric hydrate; ferric oxide hydrated; iron hydrate; iron hydroxide; iron hydroxide oxide; yellow ochre; yellow iron oxide.
(c) Iron oxide red: anhydrous ferric oxide; anhydrous iron (III) oxide; *Bayferrox 105M*; CI 77499; diiron trioxide; E172; mapico red; red ferric oxide.
(d) Iron oxide yellow monohydrate: E172; hydrated ferric oxide; iron (III) oxide monohydrate, yellow; mapico yellow; pigment yellow 42; yellow ferric oxide.

3 Chemical Name and CAS Registry Number

Iron oxides [977053-38-5]
(a) Iron oxide black [1317-61-9]
(b) Iron (III) oxide hydrated [20344-49-4]
(c) Iron oxide red [1309-37-1]
(d) Iron oxide yellow monohydrate [51274-00-1]

4 Empirical Formula and Molecular Weight

(a) Fe_3O_4	231.54
(b) $FeHO_2$	88.85
(c) Fe_2O_3	159.70
(d) $Fe_2O_3{\cdot}H_2O$	177.70

5 Structural Formula

Iron oxides are defined as inorganic compounds consisting of any one of or combinations of synthetically prepared iron oxides, including the hydrated forms.

6 Functional Category

Colorants.

7 Applications in Pharmaceutical Formulation or Technology

Iron oxides are widely used in cosmetics, foods, and pharmaceutical applications as colorants and UV absorbers.(1–3) As inorganic colorants they are becoming of increasing importance as a result of the limitations affecting some synthetic organic dyestuffs. However, iron oxides also have restrictions in some countries on the quantities that may be consumed and technically their use is restricted because of their limited color range and their abrasiveness.

8 Description

Iron oxides occur as yellow, red, black, or brown powder. The color depends on the particle size and shape, and the amount of combined water.

9 Pharmacopeial Specifications

—

10 Typical Properties

Density: 5.1 g/cm^3 for iron oxide black (Fe_3O_4)
Melting point: 1538°C for iron oxide black (Fe_3O_4)
Solubility: soluble in strong mineral acids; practically insoluble in water (for iron oxide black, Fe_3O_4).

11 Stability and Storage Conditions

Iron oxides should be stored in well-closed containers stored in a cool, dry, place.

12 Incompatibilities

Iron oxides have been reported to make hard gelatin capsules brittle at higher temperatures when the residual moisture is 11–12%. This factor affects the use of iron oxides for coloring hard gelatin capsules, and will limit the amount that can be incorporated into the gelatin material.

13 Method of Manufacture

Fe^{2+} salt solutions are precipitated and oxidized to black or brown iron oxide.

14 Safety

Iron oxides are widely used in cosmetics, foods, and oral and topical pharmaceutical applications. They are generally regarded as nontoxic and nonirritant excipients. The use of iron oxide colorants is limited in some countries, such as the USA, to a maximum ingestion of 5 mg of elemental iron per day.

For iron oxide red (Fe_2O_3):

LD_{50} (mouse, IP): 5.4 g/kg(4)
LD_{50} (rat, IP): 5.5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled. In the UK, the occupational exposure limits for iron oxide fumes (as Fe) are 5 mg/m^3 long-term (8-hour TWA) and 10 mg/m^3 short-term.(5)

16 Regulatory Status

Accepted for use as a food additive in Europe. Included in nonparenteral medicines licensed in many countries including Japan, UK, and USA.

Table I: Joint FAO/WHO Expert Committee on Food Additive specifications for iron oxides.

Test	FAO/WHO
Water-soluble matter	$\leqslant$1.0%
Barium	$\leqslant$50 mg/kg
Cadmium	$\leqslant$10 mg/kg
Chromium	$\leqslant$100 mg/kg
Copper	$\leqslant$50 mg/kg
Mercury	$\leqslant$1 mg/kg
Nickel	$\leqslant$100 mg/kg
Zinc	$\leqslant$100 mg/kg
Arsenic	$\leqslant$3 mg/kg
Lead	$\leqslant$10 mg/kg
Assay	+

17 Related Substances

—

18 Comments

The EINECS number for iron oxide red (Fe_2O_3) is 215-168-2. The EINECS number for iron oxide black (Fe_3O_4) is 215-277-5.

Although iron oxides are not included in any pharmacopeias, the Joint FAO/WHO Expert Committee on Food Additives has issued specifications for iron oxides, *see* Table I.(6) Specifications for iron oxide black,(7) iron oxide red,(8) and iron oxide yellow monohydrate(9) are included in the Japanese Pharmaceutical Excipients (JPE) 2004; *see* Table II.

Table II: Specifications for iron oxide black, iron oxide red, and iron oxide yellow monohydrate from JPE 2004.

Test	JPE 2004		
	Iron oxide black (a)	Iron oxide red (c)	Iron oxide yellow monohydrate (d)
Description	+	+	+
Identification	+	+	+
Purity	+	+	+
Heavy metals	$\leqslant$30 ppm	$\leqslant$30 ppm	$\leqslant$30 ppm
Arsenic	$\leqslant$10 ppm	$\leqslant$2 ppm	$\leqslant$2 ppm
Loss on ignition	—	—	10.0–13.0%
Water-soluble substances	+	+	+
Loss on drying	$\leqslant$1.0%	—	—
Assay	$\geqslant$90.0% (dried basis)	$\geqslant$98.0%	$\geqslant$98.0%

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20 General References

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21 Authors

LY Galichet.

22 Date of Revision

17 August 2005.

Isomalt

1 Nonproprietary Names

BP: Isomalt
PhEur: Isomaltum

2 Synonyms

GalenIQ; hydrogenated isomaltulose; hydrogenated palatinose; E953; *Isomaltidex 16500*; *Palatinit*.

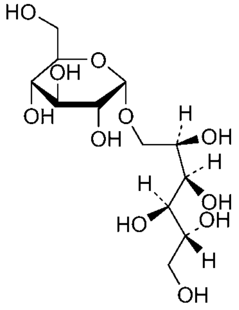
3 Chemical Name and CAS Registry Number

Isomalt [64519-82-0]
Isomalt is a mixture of two stereoisomers:
6-O-α-D-glucopyranosyl-D-sorbitol (1,6-GPS) [534-73-6]
1-O-α-D-glucopyranosyl-D-mannitol dihydrate (1,1-GPM) [20942-99-8]

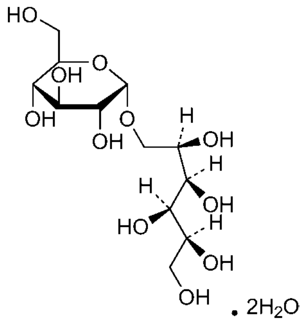
4 Empirical Formula and Molecular Weight

$C_{12}H_{24}O_{11}$	344.32 (for anhydrous)
$C_{12}H_{24}O_{11}\cdot 2H_2O$	380.32 (for dihydrate)

5 Structural Formula



$C_{12}H_{24}O_{11}$
(1,6-GPS)



$C_{12}H_{24}O_{11} \cdot 2H_2O$
(1,1-GPM)

Generally, isomalt comprises a mixture of 1,6-GPS and 1,1-GPM. 1,6-GPS crystallizes without water and is more soluble than 1,1-GPM. By shifting the ratio of the two components, the solubility and crystal water content can be adjusted, *see* Section 10. *GalenIQ 720* has a GPM : GPS ratio of 1 : 1; *GalenIQ 721* has a GPM : GPS ratio of 1 : 3.

6 Functional Category

Base for medicated confectionery; coating agent; granulating agent; sweetening agent; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Isomalt is a noncariogenic excipient used in a variety of pharmaceutical preparations including tablets or capsules, coatings, sachets, and suspensions, and in effervescent tablets. It can also be used in direct compression and wet granulation.(1)

In buccal applications such as chewable tablets it is commonly used because of its negligible negative heat of solution, mild sweetness, and 'mouth feel'.(2,3) It is also used widely in lozenges, sugar-free chewing gum, and hard-boiled candies, and as a sweetening agent in confectionery for diabetics.

See also Section 18.

8 Description

Isomalt is a sugar alcohol (polyol) that occurs as a white or almost white powder or granular or crystalline substance. It has a pleasant sugarlike taste with a mild sweetness approximately 50–60% of that of sucrose.(2–4)

9 Pharmacopeial Specifications

See Table I. *See also* Section 18.

10 Typical Properties

Angle of repose: *see* Table II.
Compressibility: compression characteristics may vary, depending on the grade of isomalt used; *see* Figure 1.
Density (bulk): *see* Table II.
Density (tapped): *see* Table II.
Density (true):
1.52 g/cm^3 for 1,6-GPS;
1.47 g/cm^3 for 1,1-GPM.
Flowability: powder is cohesive; granules are free flowing.(2)
Glass transition temperature:
63°C for a 1 : 3 mixture of 1,1-GPM and 1,6-GPS;
68°C for 1,1-GPM;
59°C for 1,6-GPS.(2)
Heat of combustion: 0.017 kJ/kg(5)
Heat of solution: +14.6 kJ/mol for an equimolar mixture of 1,1-GPM and 1,6-GPS.(2)
Hygroscopicity: not hygroscopic until 85% RH, at 25°C.(2) *See also* Figure 2.
Melting point:
141–161°C for a 1 : 3 mixture of 1,1-GPM and 1,6-GPS;
166–168°C for 1,6-GPS;
168–171°C for 1,1-GPM.(2)
Minimum ignition temperature: >460°C
Moisture content: *see* Figure 2.

Table I: Pharmacopoeial specifications for isomalt.

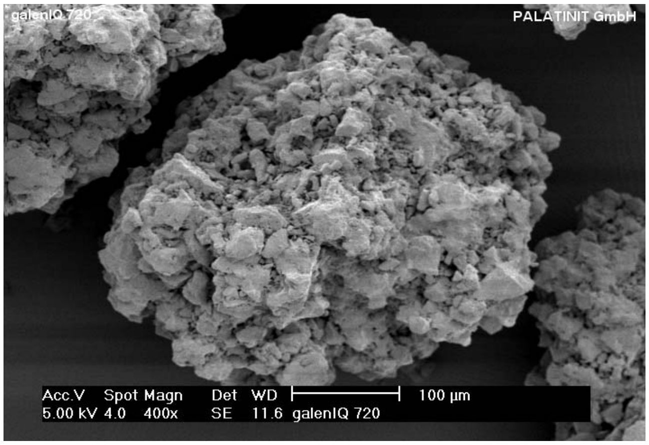
Test	PhEur 2005
Identification	+
Characters	+
Related products	+
Conductivity	≤20 µS cm^{-1}
Reducing sugars	≤0.3%
Lead	≤0.5 ppm
Nickel	≤1 ppm
Water	≤7.0%
Assay	98.0–102.0%

Particle size distribution:
approximately 90% >100 µm for *GalenIQ 720*;
approximately 58% >20 µm for *GalenIQ 800*;
approximately 99% >200 µm for *GalenIQ 960*.

pH: 3–10$^{(3)}$

Solubility: *see* Figure 3.

SEM: 1
Excipient: GalenIQ 720
Manufacturer: Palatinit GmbH
Magnification: 400×
Voltage: 5 kV


galenIQ 720
PALATINIT GmbH
Acc.V Spot Magn Det WD 100 µm
5.00 kV 4.0 400x SE 11.6 galenIQ 720

SEM: 2
Excipient: GalenIQ 721
Manufacturer: Palatinit GmbH
Magnification: 400×
Voltage: 5 kV

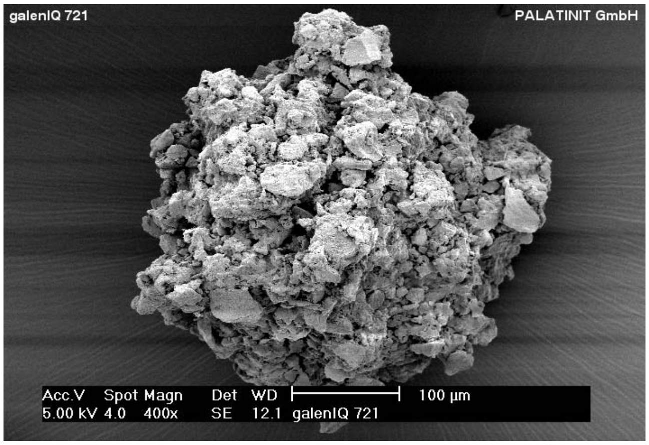
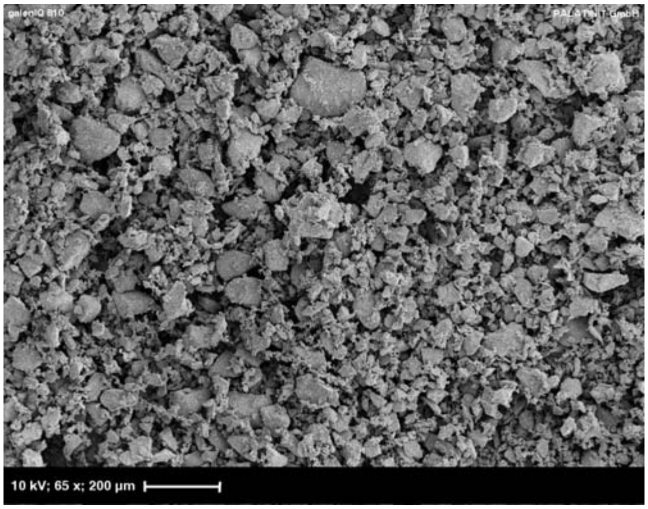

galenIQ 721
PALATINIT GmbH
Acc.V Spot Magn Det WD 100 µm
5.00 kV 4.0 400x SE 12.1 galenIQ 721

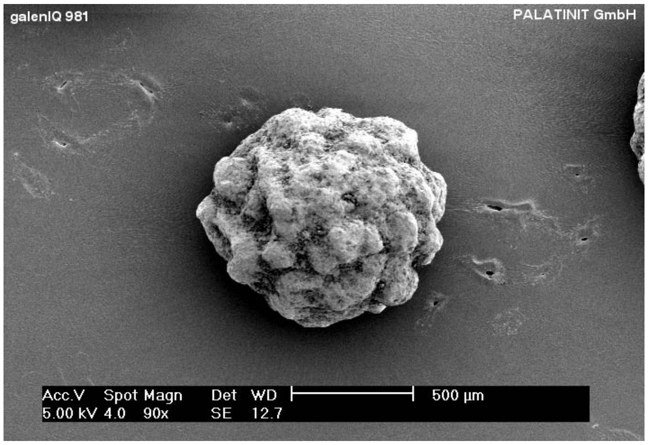
Table II: Typical physical properties of selected commercially available isomalt grades, *GalenIQ* (Palatinit GmbH).

Grade	Angle of repose (°)	Density (bulk) (g/cm^3)	Density (tapped) (g/cm^3)
GalenIQ 720	38	0.43	0.48
GalenIQ 721	37	0.42	0.45
GalenIQ 800	—	0.50	0.65
GalenIQ 810	—	0.59	0.70
GalenIQ 960	33	0.82	—
GalenIQ 980	—	0.82	—
GalenIQ 981	—	0.78	—
GalenIQ 990	—	0.85	—

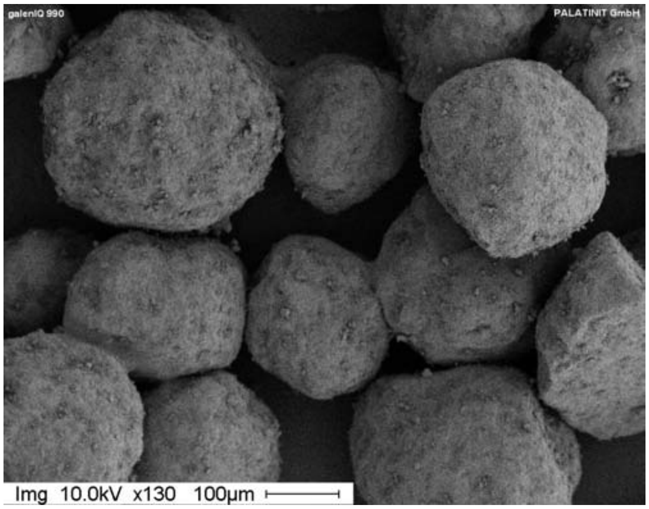
SEM: 3
Excipient: GalenIQ 810
Manufacturer: Palatinit GmbH
Magnification: 65×
*Voltage:*10 kV


galenIQ 810
PALATINIT GmbH
10 kV; 65 x; 200 µm

SEM: 4
Excipent: GalenIQ 981
Manufacturer: Palatinit GmbH
Magnification: 90×
Voltage: 5 kV


galenIQ 981
PALATINIT GmbH
Acc.V Spot Magn Det WD 500 µm
5.00 kV 4.0 90x SE 12.7

SEM: 5
Excipent: GalenIQ 990
Manufacturer: Palatinit GmbH
Magnification: 130×
Voltage: 10 kV



11 Stability and Storage Conditions

Isomalt has very good thermal and chemical stability. When it is melted, no changes in the molecular structure are observed. It exhibits considerable resistance to acids and microbial influences.(1) Isomalt is non-hygroscopic, and at 25°C does not significantly absorb additional water up to a relative humidity (RH) of 85%; paracetamol (acetaminophen) tablets based on isomalt were stored for 6 months at 85% RH at 20°C and retained their physical aspect.(1)

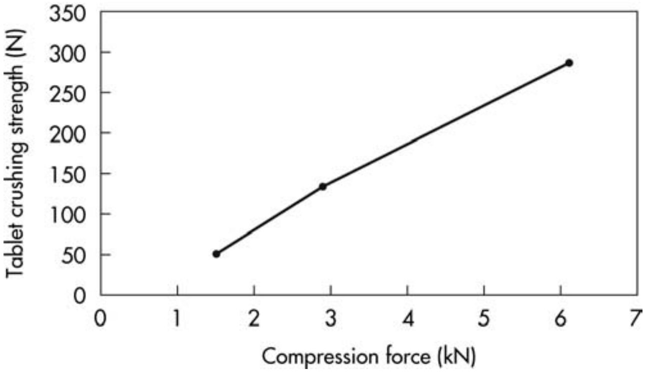


Figure 1: Tablet crushing strength of isomalt (*GalenIQ 720*, Palatinit GmbH).
Formulation: 99.5% isomalt, 0.5% magnesium stearate
Tablet weight: 240 mg
Diameter: 8 mm
Press: Fette P1200
Punch: concave

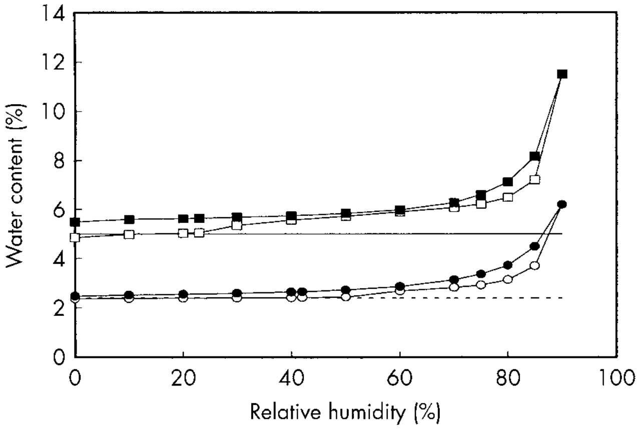


Figure 2: Sorption isotherms of isomalt DC types.[a,b]
□: Adsorption *GalenIQ 720* (Palatinit GmbH)
■: Desorption *GalenIQ 720* (Palatinit GmbH)
– – –: Crystal water *GalenIQ 720* (Palatinit GmbH)
○: Adsorption *GalenIQ 721* (Palatinit GmbH)
●: Desorption *GalenIQ 721* (Palatinit GmbH)
– – –: Crystal water *GalenIQ 721* (Palatinit GmbH)

[a] Measured using Dynamic Vapor Sorption, Südzucker AG.

[b] 1,6-GPS occurs without crystal water and 1,1-GPM crystallizes with 2 mol crystal water (the initial water content in commercial forms, *see* Section 18). The starting point of the curves depends on the water content. The content of free water in the product is typically 0.5–1.0%.

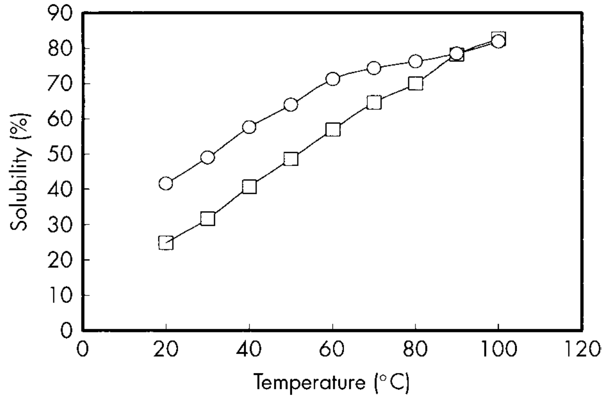


Figure 3: Solubility of isomalt types in water.(2)
□: *GalenIQ 720* (Palatinit GmbH)
○: *GalenIQ 721* (Palatinit GmbH)

If stored under normal ambient conditions, isomalt is chemically stable for many years. When it is stored in an unopened container at 20°C and 60% RH, a re-evaluation after 3 years is recommended.

Isomalt does not undergo browning reactions; it has no reducing groups, therefore it does not react with other ingredients in a formulation (e.g. with amines in Maillard reactions).

12 Incompatibilities

—

13 Method of Manufacture

Isomalt is produced from food-grade sucrose in a two-stage process. Beet sugar is converted by enzymatic transglucosidation into the reducing disaccharide isomaltulose. This undergoes catalytical hydrogenation to produce isomalt.

14 Safety

Isomalt is used in oral pharmaceutical formulations, confectionery, and food products. It is generally regarded as a nontoxic, nonallergenic, and nonirritant material.

Toxicological and metabolic studies on isomalt(5–10) have been summarized in a WHO report prepared by the FAO/WHO Expert Committee (JECFA), resulting in an acceptable daily intake of 'not specified'.(11)

The glycosidic linkage between the mannitol or sorbitol moiety and the glucose moiety is very stable, limiting the hydrolysis and absorption of isomalt in the small intestine. There is no significant increase in the blood glucose level after oral intake, and glycemic response is very low, making isomalt suitable for diabetics. The majority of isomalt is fermented in the large intestine. In general, isomalt is tolerated very well, although excessive consumption may result in laxative effects.(12–14)

Isomalt is not fermented by bacteria present in the mouth, therefore no significant amount of organic acid is produced that attacks tooth enamel.(15–17)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask or respirator are recommended.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe.

17 Related Substances

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18 Comments

Compression of isomalt without lubrication is difficult, and problems such as die wall sticking, capping, and lamination have been observed. The addition of a lubricant such as magnesium stearate will reduce die wall adhesion. Co-extrusion of isomalt with paracetamol (acetaminophen) significantly improved the tableting properties of the mixtures, compared to physical mixtures of drug and isomalt.(18) Direct molding is also a potentially suitable technique for producing isomalt-based tablets.(18)

It is anticipated that a specification for isomalt will soon be included in the USPNF.(19)

A variety of different grades of isomalt are commercially available that have different applications, e.g. *GalenIQ 720* and *721* are used in direct compression, *GalenIQ 810* is used in wet granulation, *GalenIQ 981* is used in coatings, and *GalenIQ 990* is used in boilings.

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Dörr T, Willibald-Ettle I. Evaluation of the kinetics of dissolution of tablets and lozenges consisting of saccharides and sugar substitutes. *Pharm Ind* 1996; **58**: 947–952.

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21 Authors

B Fritzsching, O Luhn, A Schoch.

22 Date of Revision

15 September 2005.

Isopropyl Alcohol

1 Nonproprietary Names

BP: Isopropyl alcohol
JP: Isopropanol
PhEur: Alcohol isopropylicus
USP: Isopropyl alcohol

2 Synonyms

Dimethyl carbinol; IPA; isopropanol; petrohol; 2-propanol; *sec*-propyl alcohol.

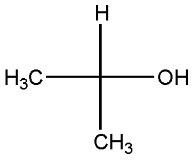
3 Chemical Name and CAS Registry Number

Propan-2-ol [67-63-0]

4 Empirical Formula and Molecular Weight

C_3H_8O 60.1

5 Structural Formula



6 Functional Category

Disinfectant; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Isopropyl alcohol (propan-2-ol) is used in cosmetics and pharmaceutical formulations primarily as a solvent in topical formulations.(1) It is not recommended for oral use owing to its toxicity; *see* Section 14.

Although it is used in lotions, the marked degreasing properties of isopropyl alcohol may limit its usefulness in preparations used repeatedly. Isopropyl alcohol is also used as a solvent both for tablet film-coating and for tablet granulation,(2) where the isopropyl alcohol is subsequently removed by evaporation. It has also been shown to significantly increase the skin permeability of nimesulide from carbomer 934.(3)

Isopropyl alcohol has some antimicrobial activity (*see* Section 10) and a 70% v/v aqueous solution is used as a topical disinfectant. Therapeutically, isopropyl alcohol has been investigated for the treatment of postoperative nausea or vomiting.(4)

8 Description

Isopropyl alcohol is a clear, colorless, mobile, volatile, flammable liquid with a characteristic, spirituous odor resembling that of a mixture of ethanol and acetone; it has a slightly bitter taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for isopropyl alcohol.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Appearance of solution	—	+	—
Absorbance	—	+	—
Characters	—	+	+
Specific gravity	0.785–0.788	0.785–0.789	0.783–0.787
Refractive index	—	1.376–1.379	1.376–1.378
Acidity or alkalinity	+	+	+
Water	⩽0.75%	⩽0.5%	—
Nonvolatile residue	⩽1.0 mg	⩽20 ppm	⩽0.005%
Distillation range	81–83°C	—	—
Benzene	—	+	—
Peroxides	—	+	—
Assay	—	—	⩾99.0%

10 Typical Properties

Antimicrobial activity: isopropyl alcohol is bactericidal; at concentrations greater than 70% v/v it is a more effective antibacterial preservative than ethanol (95%). The bactericidal effect of aqueous solutions increases steadily as the concentration approaches 100% v/v. Isopropyl alcohol is ineffective against bacterial spores.

Autoignition temperature: 425°C

Boiling point: 82.4°C

Dielectric constant: $D^{20} = 18.62$

Explosive limits: 2.5–12.0% v/v in air.

Flammability: flammable.

Flash point: 11.7°C (closed cup); 13°C (open cup). The water azeotrope has a flash point of 16°C.

Freezing point: −89.5°C

Melting point: −88.5°C

Moisture content: 0.1–13% w/w for commercial grades (13% w/w corresponds to the water azeotrope).

Refractive index:
$n_D^{20} = 1.3776$;
$n_D^{25} = 1.3749$.

Solubility: miscible with benzene, chloroform, ethanol (95%), ether, glycerin, and water. Soluble in acetone; insoluble in salt solutions. Forms an azeotrope with water, containing 87.4% w/w isopropyl alcohol (boiling point 80.37°C).

Specific gravity: 0.786

Vapor density (relative): 2.07 (air = 1)

Vapor pressure:
133.3 Pa (1 mmHg) at −26.1°C;
4.32 kPa (32.4 mmHg) at 20°C;
5.33 kPa (40 mmHg) at 23.8°C;
13.33 kPa (100 mmHg) at 39.5°C.

Viscosity (dynamic): 2.43 mPa s (2.43 cP) at 20°C

11 Stability and Storage Conditions

Isopropyl alcohol should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid, which cause decomposition. Isopropyl alcohol may be salted out from aqueous mixtures by the addition of sodium chloride, sodium sulfate, and other salts, or by the addition of sodium hydroxide.

13 Method of Manufacture

Isopropyl alcohol may be prepared from propylene; by the catalytic reduction of acetone, or by fermentation of certain carbohydrates.

14 Safety

Isopropyl alcohol is widely used in cosmetics and topical pharmaceutical formulations. It is readily absorbed from the gastrointestinal tract and may be slowly absorbed through intact skin. Prolonged direct exposure of isopropyl alcohol to the skin may result in cardiac and neurological deficits.(5) In neonates, isopropyl alcohol has been reported to cause chemical burns following topical application.(6,7)

Isopropyl alcohol is metabolized more slowly than ethanol, primarily to acetone. Metabolites and unchanged isopropyl alcohol are mainly excreted in the urine.

Isopropyl alcohol is about twice as toxic as ethanol and should therefore not be administered orally; isopropyl alcohol also has an unpleasant taste. Symptoms of isopropyl alcohol toxicity are similar to those for ethanol except that isopropyl alcohol has no initial euphoric action and gastritis and vomiting are more prominent; *see* Alcohol. Delta osmolality may be useful as rapid screen test to identify patients at risk of complications from ingestion of isopropyl alcohol.(8) The lethal oral dose is estimated to be about 120–250 mL although toxic symptoms may be produced by 20 mL.

Adverse effects following parenteral administration of up to 20 mL of isopropyl alcohol diluted with water have included only a sensation of heat and a slight lowering of blood pressure. However, isopropyl alcohol is not commonly used in parenteral products.

Although inhalation can cause irritation and coma, the inhalation of isopropyl alcohol has been investigated in therapeutic applications.(3)

Isopropyl alcohol is most frequently used in topical pharmaceutical formulations where it may act as a local irritant.(9) When applied to the eye it can cause corneal burns and eye damage.

LD_{50} (dog, oral): 4.80 g/kg(9)
LD_{50} (mouse, oral): 3.6 g/kg
LD_{50} (mouse, IP): 4.48 g/kg
LD_{50} (mouse, IV): 1.51 g/kg
LD_{50} (rabbit, oral): 6.41 g/kg
LD_{50} (rabbit, skin): 12.8 g/kg
LD_{50} (rat, IP): 2.74 g/kg
LD_{50} (rat, IV): 1.09 g/kg
LD_{50} (rat, oral): 5.05 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Isopropyl alcohol may be irritant to the skin, eyes, and mucous membranes upon inhalation. Eye protection and gloves are recommended. Isopropyl alcohol should be handled in a well-ventilated environment. In the UK, the long-term (8-hour TWA) exposure limit for isopropyl alcohol is 999 mg/m^3 (400 ppm); the short-term (15-minute) exposure limit is 1250 mg/m^3 (500 ppm).(10) OSHA standards state that IPA 8-hour time weighted average airborne level in the workplace cannot exceed 400 ppm. Isopropyl alcohol is flammable and produces toxic fumes on combustion.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules, tablets, and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Propan-1-ol.

Propan-1-ol

Empirical formula: C_3H_8O
Molecular weight: 60.1
CAS number: [71-23-8]
Synonyms: propanol; *n*-propanol; propyl alcohol; propylic alcohol.
Autoignition temperature: 540°C
Boiling point: 97.2°C
Dielectric constant: $D^{25} = 22.20$
Explosive limits: 2.15–13.15% v/v in air.
Flash point: 15°C (closed cup)
Melting point: –127°C
Refractive index: $n_D^{20} = 1.3862$
Solubility: miscible with ethanol (95%), ether, and water.
Specific gravity: 0.8053 at 20°C
Viscosity (dynamic): 2.3 mPa s (2.3 cP) at 20°C
Comments: propan-1-ol is more toxic than isopropyl alcohol. In the UK, the long-term (8-hour TWA) exposure limit for propan-1-ol is 500 mg/m^3 (200 ppm); the short-term (15-minute) exposure limit is 625 mg/m^3 (250 ppm).(10)

18 Comments

A specification for isopropyl alcohol is contained in the Food Chemicals Codex (FCC).

The EINECS number for isopropyl alcohol is 200-661-7.

19 Specific References

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4 Merritt BA, Okyere CP, Jasinski DM. Isopropyl alcohol inhalation: alternative treatment of postoperative nausea and vomiting. *Nurs Res* 2002; **51**(2): 125–128.

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20 General References

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21 Authors

CP McCoy.

22 Date of Revision

12 August 2005.

Isopropyl Myristate

1 Nonproprietary Names

BP: Isopropyl myristate
PhEur: Isopropylis myristas
USPNF: Isopropyl myristate

2 Synonyms

Crodamol IPM; *Estol IPM*; isopropyl ester of myristic acid; *Kessco IPM 95*; *Lexol IPM-NF*; myristic acid isopropyl ester; *Rita IPM*; *Stepan IPM*; *Tegosoft M*; tetradecanoic acid, 1-methylethyl ester; *Waglinol 6014*.

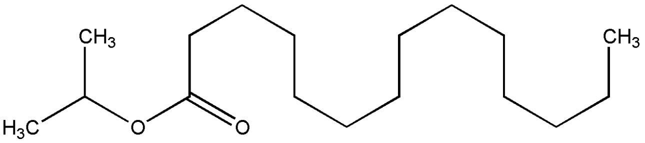
3 Chemical Name and CAS Registry Number

1-Methylethyl tetradecanoate [110-27-0]

4 Empirical Formula and Molecular Weight

$C_{17}H_{34}O_2$ 270.5

5 Structural Formula



6 Functional Category

Emollient; oleaginous vehicle; skin penetrant; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Isopropyl myristate is a nongreasy emollient that is absorbed readily by the skin. It is used as a component of semisolid bases and as a solvent for many substances applied topically. Applications in topical pharmaceutical and cosmetic formulations include bath oils; make-up; hair and nail care products; creams; lotions; lip products; shaving products; skin lubricants; deodorants; otic suspensions; and vaginal creams; *see* Table I. For example, isopropyl myristate is a self-emulsifying component of a proposed cold cream formula,(1) which is suitable for use as a vehicle for drugs or dermatological actives; it is also used cosmetically in stable mixtures of water and glycerol.(2)

Isopropyl myristate is used as a penetration enhancer for transdermal formulations and has been used in conjunction with therapeutic ultrasound and iontophoresis.(3) It has been used in a water-oil gel prolonged-release emulsion and in various microemulsions. Isopropyl myristate has also been used in microspheres, and significantly increased the release of drug from etoposide-loaded microspheres.(4)

Table I: Uses of isopropyl myristate.

Use	Concentration (%)
Detergent	0.003–0.03
Otic suspension	0.024
Perfumes	0.5–2.0
Microemulsions	<50
Soap	0.03–0.3
Topical aerosols	2.0–98.0
Topical creams and lotions	1.0–10.0

8 Description

Isopropyl myristate is a clear, colorless, practically odorless liquid of low viscosity that congeals at about 5°C. It consists of esters of propan-2-ol and saturated high molecular weight fatty acids, principally myristic acid.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for isopropyl myristate.

Test	PhEur 2005	USPNF 23
Identification	+	+
Appearance of solution	+	—
Specific gravity	—	0.846–0.854
Relative density	≈0.853	0.846–0.854
Refractive index	1.434–1.437	1.432–1.436
Residue on ignition	⩽0.1%	⩽0.1%
Acid value	⩽1.0	⩽1.0
Saponification value	202–212	202–212
Iodine value	⩽1.0	⩽1.0
Appearance of solution	+	—
Viscosity	5–6 mPa s	—
Water	⩽0.1%	—
Organic volatile impurities	—	+
Assay (as $C_{17}H_{34}O_2$)	⩾90.0%	⩾90.0%

10 Typical Properties

Boiling point: 140.2°C at 266 Pa (2 mmHg)
Flash point: 153.5°C (closed cup)
Freezing point: ≈5°C
Solubility: soluble in acetone, chloroform, ethanol (95%), ethyl acetate, fats, fatty alcohols, fixed oils, liquid hydrocarbons, toluene, and waxes. Dissolves many waxes, cholesterol, or lanolin. Practically insoluble in glycerin, glycols, and water.
Viscosity (dynamic): 5–7 mPa s (5–7 cP) at 25°C

11 Stability and Storage Conditions

Isopropyl myristate is resistant to oxidation and hydrolysis and does not become rancid. It should be stored in a well-closed container in a cool, dry place and protected from light.

12 Incompatibilities

When isopropyl myristate comes into contact with rubber, there is a drop in viscosity with concomitant swelling and partial dissolution of the rubber; contact with plastics, e.g. nylon and polyethylene, results in swelling. Isopropyl myristate is incompatible with hard paraffin, producing a granular mixture. It is also incompatible with strong oxidizing agents.

13 Method of Manufacture

Isopropyl myristate may be prepared either by the esterification of myristic acid with propan-2-ol or by the reaction of myristoyl chloride and propan-2-ol with the aid of a suitable dehydrochlorinating agent. A high-purity material is also commercially available, produced by enzymatic esterification at low temperature.

14 Safety

Isopropyl myristate is widely used in cosmetics and topical pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material.(5–7)

LD_{50} (mouse, oral): 49.7 g/kg(8)
LD_{50} (rabbit, skin): 5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (otic, topical, transdermal, and vaginal preparations). Used in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Isopropyl palmitate.

18 Comments

The EINECS number for isopropyl myristate is 203-751-4.

19 Specific References

1 Jimenez SMM, Fresno CMJ, Selles Flores E. Proposal and pharmacotechnical study of a modern dermo-pharmaceutical formulation for cold cream. *Boll Chim Farm* 1996; **135**: 364–373.
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3 Fang JY, Fang CL, Huang YB. Transdermal iontopheresis of sodium nonivaride acetate III: combined effect of pretreatment by penetration enhancers. *Int J Pharm* 1997; **149**: 183–195.
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20 General References

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Nakhare S, Vyas SP. Prolonged release of rifampicin from internal phase of multiple w/o/w emulsion systems. *Indian J Pharm Sci* 1995; **57**: 71–77.

21 Authors

AK Taylor.

22 Date of Revision

16 August 2005.

Isopropyl Palmitate

1 Nonproprietary Names

BP: Isopropyl palmitate
PhEur: Isopropylis palmitas
USPNF: Isopropyl palmitate

2 Synonyms

Crodamol IPP; *Emerest 2316*; hexadecanoic acid isopropyl ester; hexadecanoic acid 1-methylethyl ester; isopropyl hexadecanoate; *Kessco IPP*; *Lexol IPP-NF*; *Liponate IPP*; palmitic acid isopropyl ester; *Protachem IPP*; *Rita IPP*; *Stepan IPP*; *Tegosoft P*; *Unimate IPP*; *Waglinol 6016*; *Wickenol 111*.

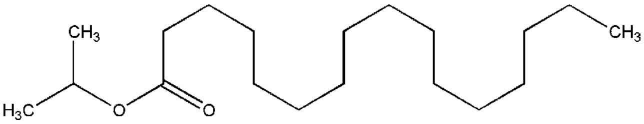
3 Chemical Name and CAS Registry Number

1-Methylethyl hexadecanoate [142-91-6]

4 Empirical Formula and Molecular Weight

$C_{19}H_{38}O_2$ 298.51

5 Structural Formula



6 Functional Category

Emollient; oleaginous vehicle; skin penetrant; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Isopropyl palmitate is a nongreasy emollient with good spreading characteristics, used in topical pharmaceutical formulations and cosmetics such as: bath oils; creams; lotions; make-up; hair care products; deodorants; lip products; suntan preparations; and pressed powders; *see* Table I.

Isopropyl palmitate has also been used in controlled-release percutaneous films, and has also been investigated in the production of reversed sucrose ester vesicles, as well as microemulsions.(1)

Table I: Uses of isopropyl palmitate.

Use	Concentration (%)
Detergent	0.005–0.02
Perfume	0.2–0.8
Soap	0.05–0.2
Topical aerosol spray	3.36
Topical creams and lotions	0.05–5.5

8 Description

Isopropyl palmitate is a clear, colorless to pale yellow-colored, practically odorless viscous liquid that solidifies at less than 16°C.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for isopropyl palmitate.

Test	PhEur 2005	USPNF 23
Identification	+	+
Acid value	$\leqslant 1.0$	$\leqslant 1.0$
Appearance of solution	+	—
Characters	—	+
Iodine value	$\leqslant 1.0$	$\leqslant 1.0$
Organic volatile impurities	—	+
Relative density	0.850–0.855	0.850–0.855
Residue on ignition	$\leqslant 0.1\%$	$\leqslant 0.1\%$
Refractive index	1.436–1.440	1.435–1.438
Saponification value	183–193	183–193
Viscosity	5–10 mPa s	—
Water	$\leqslant 0.1\%$	—
Assay (of $C_{19}H_{38}O_2$)	$\geqslant 90.0\%$	$\geqslant 90.0\%$

10 Typical Properties

Boiling point: 160°C at 266 Pa (2 mmHg)
Freezing point: $\approx$13–15°C
Solubility: soluble in acetone, chloroform, ethanol (95%), ethyl acetate, mineral oil, propan-2-ol, silicone oils, vegetable oils, and aliphatic and aromatic hydrocarbons; practically insoluble in glycerin, glycols, and water.
Surface tension: $\approx$29 mN/m for *Tegosoft P* at 25°C
Viscosity (dynamic): 5–10 mPa s (5–10 cP) at 25°C

11 Stability and Storage Conditions

Isopropyl palmitate is resistant to oxidation and hydrolysis and does not become rancid. It should be stored in a well-closed container, above 16°C, and protected from light.

12 Incompatibilities

See Isopropyl Myristate.

13 Method of Manufacture

Isopropyl palmitate is prepared by the reaction of palmitic acid with propan-2-ol in the presence of an acid catalyst. A high-purity material is also commercially available, which is produced by enzymatic esterification at low temperatures.

14 Safety

Isopropyl palmitate is widely used in cosmetics and topical pharmaceutical formulations, and is generally regarded as a relatively nontoxic and nonirritant material.(2–4)

LD_{50} (mouse, IP): 0.1 g/kg(5)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (topical and transdermal preparations). Used in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Isopropyl myristate.

18 Comments

The EINECS number for isopropyl palmitate is 205-571-1.

19 Specific References

1 Mollee H, De Vrind J, De Vringer T. Stable reversed vesicles in oil: characterization studies and encapsulation of model compounds. *J Pharm Sci* 2000; **89**(7): 930–939.
2 Frosch PJ, Kligman AM. The chamber-scarification test for irritancy. *Contact Dermatitis* 1976; **2**: 314–324.
3 Guillot JP, Martini MC, Giauffret JY. Safety evaluation of cosmetic raw materials. *J Soc Cosmet Chem* 1977; **28**: 377–393.
4 Opdyke DL, Letizia C. Monographs on fragrance raw materials. *Food Cosmet Toxicol* 1982; **20** (Suppl.): 633–852.
5 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 2165.

20 General References

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21 Authors

AK Taylor.

22 Date of Revision

18 August 2005.

Kaolin

1 Nonproprietary Names

BP: Heavy kaolin
JP: Kaolin
PhEur: Kaolinum ponderosum
USP: Kaolin
Note that the PhEur 2005 contains a monograph on heavy kaolin (kaolinum ponderosum). The BP 2004 in addition to the monograph for heavy kaolin also contains monographs for light kaolin (natural) and light kaolin.
See also Sections 4 and 9.

2 Synonyms

Argilla; bolus alba; China clay; E559; kaolinite; *Lion*; porcelain clay; *Sim 90*; weisserton; white bole.

3 Chemical Name and CAS Registry Number

Hydrated aluminum silicate [1332-58-7]

4 Empirical Formula and Molecular Weight

$Al_2H_4O_9Si_2$ 258.16

The USP 28 describes kaolin as a native hydrated aluminum silicate, powdered and freed from gritty particles by elutriation. The BP 2004 similarly describes light kaolin but additionally states that it contains a suitable dispersing agent. Light kaolin (natural) BP contains no dispersing agent. Heavy kaolin is described in the BP 2004 and PhEur 2005 as a purified, natural hydrated aluminum silicate of variable composition. The JP 2001 describes kaolin as a native hydrous aluminum silicate.

5 Structural Formula

$Al_2O_3{\cdot}2SiO_2{\cdot}2H_2O$

6 Functional Category

Adsorbent; suspending agent; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

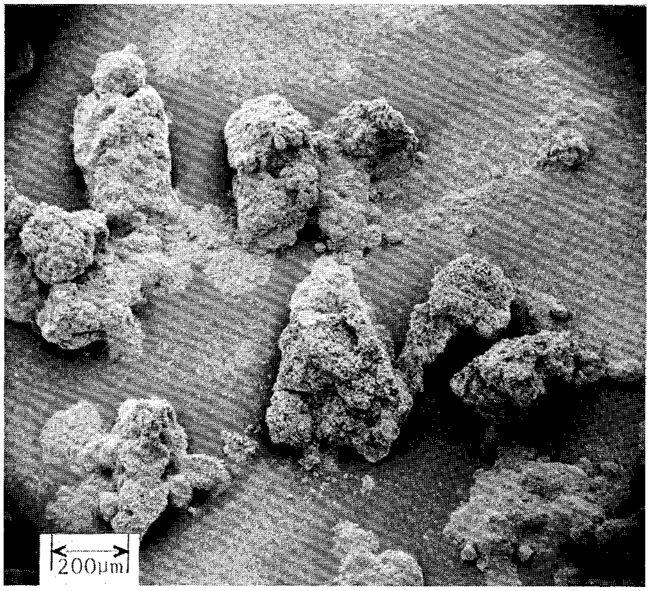
Kaolin is a naturally occurring mineral used in oral and topical pharmaceutical formulations.

In oral medicines, kaolin has been used as a diluent in tablet and capsule formulations; it has also been used as a suspending vehicle. In topical preparations, sterilized kaolin has been used in poultices and as a dusting powder. Therapeutically, kaolin has been used in oral antidiarrheal preparations.(1,2)

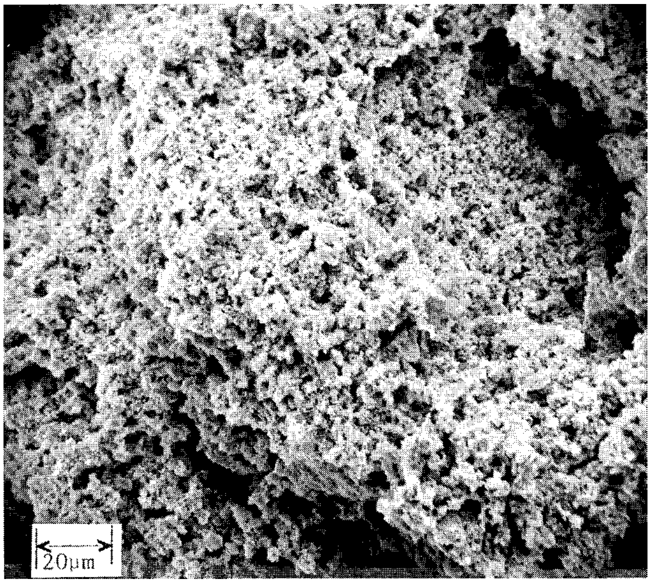
8 Description

Kaolin occurs as a white to grayish-white colored, unctuous powder free from gritty particles. It has a characteristic earthy or claylike taste and when moistened with water it becomes darker in color and develops a claylike odor.

SEM: 1
Excipient: Kaolin USP
Manufacturer: Georgia Kaolin Co.
Lot No.: 1672
Magnification: 60×
Voltage: 10 kV



SEM: 2
Excipient: Kaolin USP
Manufacturer: Georgia Kaolin Co.
Lot No.: 1672
Magnification: 600×
Voltage: 10 kV



9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for kaolin.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	—	+	—
Acidity or alkalinity	+	+	—
Microbial limit	—	≤10^3/g	+
Loss on ignition	≤15.0%	—	≤15.0%
Acid-soluble substances	+	≤1.0%	≤2.0%
Organic impurities	—	+	—
Foreign matter	+	—	—
Adsorption power	—	+	—
Swelling power	—	+	—
Plasticity	+	—	—
Arsenic	≤2 ppm	—	—
Calcium	—	≤250 ppm	—
Carbonate	+	—	+
Chloride	—	≤250 ppm	—
Heavy metals	≤50 ppm	≤50 ppm[a]	—
Iron	≤500 ppm	—	+
Lead	—	—	≤0.001%
Sulfate	—	≤0.1%	—
Organic volatile impurities	—	—	+

[a] When intended for internal use, the limit is set at ≤25 ppm.

10 Typical Properties

Acidity/alkalinity: pH = 4.0–7.5 for a 20% w/v aqueous slurry.
Hardness (Mohs): 2.0, very low.
Hygroscopicity: at relative humidities between about 15–65%, the equilibrium moisture content at 25°C is about 1% w/w, but at relative humidities above about 75%, kaolin absorbs small amounts of moisture.
Particle size distribution: median size = 0.6–0.8 μm.
Refractive index: 1.56
Solubility: practically insoluble in diethyl ether, ethanol (95%), water, other organic solvents, cold dilute acids, and solutions of alkali hydroxides.
Specific gravity: 2.6
Viscosity (dynamic): 300 mPa s (300 cP) for a 70% w/v aqueous suspension.
Whiteness: 85–90% of the brightness of MgO.

11 Stability and Storage Conditions

Kaolin is a stable material. Since it is a naturally occurring material, kaolin is commonly contaminated with microorganisms such as *Bacillus anthracis*, *Clostridium tetani*, and *Clostridium welchii*. However, kaolin may be sterilized by heating at a temperature greater than 160°C for not less than 1 hour. When moistened with water kaolin darkens and becomes plastic.

Kaolin should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

The adsorbent properties of kaolin may influence the absorption of other orally administered drugs. Drugs reportedly affected by kaolin include amoxicillin;(3) ampicillin;(3) cimetidine;(4) digoxin;(5) lincomycin; phenytoin;(6) and tetracycline. Warfarin absorption by rat intestine *in vitro* was reported not to be affected by kaolin.(7) With clindamycin, the rate (but not the amount) of absorption was affected by kaolin.(8)

13 Method of Manufacture

Kaolin is a hydrated aluminum silicate obtained by mining naturally occurring mineral deposits. Large deposits are found in Georgia, USA and in Cornwall, England.

Mined kaolin is powdered and freed of coarse, gritty particles either by elutriation or by screening. Impurities such as ferric oxide, calcium carbonate, and magnesium carbonate are removed with an electromagnet and by treatment with hydrochloric acid and/or sulfuric acids.

14 Safety

Kaolin is used in oral and topical pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material.

Oral doses of about 2–6 g of kaolin every 4 hours have been administered in the treatment of diarrhea.(1,2)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. The chronic inhalation of kaolin dust can cause diseases of the lung (silicosis or kaolinosis).(9) Eye protection and a dust mask are recommended. In the UK, the long-term (8-hour TWA) exposure limit for kaolin respirable dust is 2 mg/m^3.(10)

16 Regulatory Status

Accepted in Europe as a food additive in certain applications. Included in the FDA Inactive Ingredients Guide (oral capsules, powders, syrups, and tablets; topical preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Bentonite; magnesium aluminum silicate.

18 Comments

Kaolin is considered in most countries to be an archaic diluent.

The name kaolinite was historically used to describe the processed mineral, while the name kaolin was used for the unprocessed clay. However, the two names have effectively become synonymous and kaolin is now generally the only name used. A specification for kaolin is contained in the Food Chemicals Codex (FCC). The EINECS number for kaolin is 310-127-6.

19 Specific References

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2 Sweetman SC, ed. *Martindale: The Complete Drug Reference*, 34th edn. London: Pharmaceutical Press, 2005: 1268.
3 Khalil SAH, Mortada LM, El-Khawas M. Decreased bioavailability of ampicillin and amoxicillin in presence of kaolin. *Int J Pharm* 1984; **19**: 233–238.

4 Ganjian F, Cutie AJ, Jochsberger T. *In vitro* adsorption studies of cimetidine. *J Pharm Sci* 1980; **69**: 352–353.

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6 McElnay JC, D'Arcy PF, Throne O. Effect of antacid constituents, kaolin and calcium citrate on phenytoin absorption. *Int J Pharm* 1980; **7**: 83–88.

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8 Albert KS, DeSante KA, Welch RD, DiSanto AR. Pharmacokinetic evaluation of a drug interaction between kaolin-pectin and clindamycin. *J Pharm Sci* 1978; **67**: 1579–1582.

9 Lesser M, Zia M, Kilburn KH. Silicosis in kaolin workers and firebrick makers. *South Med J* 1978; **71**: 1242–1246.

10 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.

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Allwood MC. The adsorption of esters of *p*-hydroxybenzoic acid by magnesium trisilicate. *Int J Pharm* 1982; **11**: 101–107.

Onyekweli AO, Usifoh CO, Okunrobo LO, Zuofa JD. Adsorptive property of kaolin in some drug formulations. *Trop J Pharm Res* 2003; **2**: 155–159.

21 Authors

A Palmieri.

22 Date of Revision

7 June 2005.

Lactic Acid

1 Nonproprietary Names

BP: Lactic acid
JP: Lactic acid
PhEur: Acidum lacticum
USP: Lactic acid

2 Synonyms

E270; *Eco-Lac*; 2-hydroxypropanoic acid; α-hydroxypropionic acid; DL-lactic acid; *Lexalt L*; milk acid; *Patlac LA*; *Purac 88 PH*; racemic lactic acid.

3 Chemical Name and CAS Registry Number

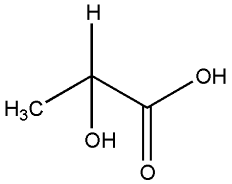
2-Hydroxypropionic acid [50-21-5]
(*R*)-(−)-2-Hydroxypropionic acid [10326-41-7]
(*S*)-(+)-2-Hydroxypropionic acid [79-33-44]
(*RS*)-(±)-2-Hydroxypropionic acid [598-82-3]

See also Section 8.

4 Empirical Formula and Molecular Weight

$C_3H_6O_3$ 90.08

5 Structural Formula



6 Functional Category

Acidifying agent; acidulant.

7 Applications in Pharmaceutical Formulation or Technology

Lactic acid is used in beverages, foods, cosmetics, and pharmaceuticals (*see* Table I) as an acidifying agent and acidulant.

In topical formulations, particularly cosmetics, it is used for its softening and conditioning effect on the skin. Lactic acid may also be used in the production of biodegradable polymers and microspheres, such as poly(D-lactic acid), used in drug delivery systems.(1,2) *See also* Aliphatic Polyesters.

Lactic acid is also used as a food preservative. Therapeutically, lactic acid is used in injections, in the form of lactate, as a source of bicarbonate for the treatment of metabolic acidosis; as a spermicidal agent; in pessaries for the treatment of leukorrhea; in infant feeds; and in topical formulations for the treatment of warts.

Table I: Uses of lactic acid.

Use	Concentration (%)
Injections	0.012–1.16
Topical preparations	0.015–6.6

8 Description

Lactic acid consists of a mixture of 2-hydroxypropionic acid, its condensation products, such as lactoyllactic acid and other polylactic acids, and water. It is usually in the form of the racemate, (*RS*)-lactic acid, but in some cases the (*S*)-(+)-isomer is predominant.

Lactic acid is a practically odorless, colorless or slightly yellow-colored, viscous, hygroscopic, nonvolatile liquid.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for lactic acid.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Appearance of solution	—	+	—
Specific rotation	—	—	−0.05° to +0.05°
Calcium	—	⩽200 ppm	—
Heavy metals	⩽10 ppm	⩽10 ppm	⩽0.001%
Iron	⩽5 ppm	—	—
Sulfate	⩽0.01%	⩽200 ppm	+
Chloride	⩽0.036%	—	+
Citric, oxalic, phosphoric, and tartaric acids	+	+	+
Ether-insoluble substances	—	+	—
Cyanide	+	—	—
Sugars and other reducing substances	+	+	+
Glycerin and mannitol	+	—	—
Methanol and methyl esters	—	⩽50 ppm	—
Reducing substances	—	+	—
Readily carbonizable substances	+	—	+
Bacterial endotoxins	—	⩽5 IU/g	—
Volatile fatty acids	+	+	—
Residue on ignition	⩽0.1%	⩽0.1%	⩽3.0 mg
Sulfated ash	—	⩽0.1%	⩽0.05%
Assay	+	88.0–92.0%	88.0–92.0%

10 Typical Properties

Boiling point: 122°C at 2 kPa (15 mmHg)
Dissociation constant: $pK_a = 4.14$ at 22.5°C
Flash point: >110°C
Heat of combustion: 15.13 kJ/kg (3615 cal/kg)
Melting point: 17°C

Osmolarity: a 2.3% w/v aqueous solution is isoosmotic with serum.

Refractive index: $n_D^{20} = 1.4251$

Solubility: miscible with ethanol (95%), ether, and water; practically insoluble in chloroform.

Specific heat: 2.11 J/g (0.505 cal/g) at 20°C

Specific gravity: 1.21

Specific rotation $[\alpha]_D^{21}$**:**

−2.6° (8% w/v aqueous solution) for (*R*)-form;

+2.6° (2.5% w/v aqueous solution) for (*S*)-form.

Viscosity (dynamic): 28.5 mPa s (28.5 cP) for 85% aqueous solution at 25°C.

11 Stability and Storage Conditions

Lactic acid is hygroscopic and will form condensation products such as polylactic acids on contact with water. The equilibrium between the polylactic acids and lactic acid is dependent on concentration and temperature. At elevated temperatures lactic acid will form lactide, which is readily hydrolyzed back to lactic acid.

Lactic acid should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatible with oxidizing agents, iodides, and albumin. Reacts violently with hydrofluoric acid and nitric acid.

13 Method of Manufacture

Lactic acid is prepared by the fermentation of carbohydrates, such as glucose, sucrose, and lactose, with *Bacillus acidi lacti* or related microorganisms. On a commercial scale, whey, corn starch, potatoes, or molasses are used as a source of carbohydrate. Lactic acid may also be prepared synthetically by the reaction between acetaldehyde and carbon monoxide at 130–200°C under high pressure, or by the hydrolysis of hexoses with sodium hydroxide.

Lactic acid prepared by the fermentation of sugars is levorotatory; lactic acid prepared synthetically is racemic. However, lactic acid prepared by fermentation becomes dextrorotatory on dilution with water owing to the hydrolysis of (*R*)-lactic acid lactate to (*S*)-lactic acid.

14 Safety

Lactic acid occurs in appreciable quantities in the body as an end product of the anaerobic metabolism of carbohydrates and, while harmful in the concentrated form (*see* Section 15), can be considered nontoxic at the levels at which it is used as an excipient. A 1% v/v solution, for example, is harmless when applied to the skin.

There is evidence that neonates have difficulty in metabolizing (*R*)-lactic acid and this isomer and the racemate should therefore not be used in foods intended for infants aged less than 3 months old.(3)

There is no evidence that lactic acid is carcinogenic, teratogenic, or mutagenic.

LD_{50} (guinea pig, oral): 1.81 g/kg(4)
LD_{50} (mouse, oral): 4.88 g/kg
LD_{50} (mouse, SC): 4.5 g/kg
LD_{50} (rat, oral): 3.73 g/kg

15 Handling Precautions

Lactic acid is caustic in concentrated form and can cause burns on contact with the skin and eyes. It is harmful if swallowed, inhaled, or absorbed through the skin. Observe precautions appropriate to the circumstances and quantity of material handled. Eye protection, rubber gloves, and respirator are recommended. It is advisable to handle the compound in a chemical fume hood and to avoid repeated or prolonged exposure. Spillages should be diluted with copious quantities of water. In case of excessive inhalation, remove the patient to a well-ventilated environment and seek medical attention. Lactic acid presents no fire or explosion hazard but emits acrid smoke and fumes when heated to decomposition.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IM, IV, and SC injections, oral syrups and tablets, topical and vaginal preparations). Included in medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Aliphatic polyesters; sodium lactate.

18 Comments

A specification for lactic acid is contained in the Food Chemicals Codex (FCC). The EINECS number for lactic acid is 200-018-0.

19 Specific References

1 Brophy MR, Deasy P. Biodegradable polyester polymers as drug carriers. In: Swarbrick J, Boylan JC, eds. *Encyclopedia of Pharmaceutical Technology,* vol. 2. New York: Marcel Dekker, 1990: 1–25.
2 Kim IS, Jeong YI, Cho CS, Kim SH. Core–shell type polymeric nanoparticles composed of poly(L-lactic acid) and poly(*N*-isopropylacrylamide). *Int J Pharm* 2000; **211**: 1–8.
3 FAO/WHO. Toxicological evaluation of certain food additives with a review of general principles and specifications. Seventeenth report of the FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1974; No. 539.
4 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 2196.

20 General References

Al-Shammary FJ, Mian NAZ, Mian MS. Lactic acid. In: Brittain HG, ed. *Analytical Profiles of Drug Substances and Excipients,* vol. 22. San Diego: Academic Press, 1993: 263–316.

21 Authors

MG Lee.

22 Date of Revision

15 August 2005.

Lactitol

1 Nonproprietary Names

BP: Lactitol monohydrate
PhEur: Lactitolum monohydricum
USPNF: Lactitol

2 Synonyms

E966; β-galactosido-sorbitol; *Finlac DC*; lactil; lactite; lactobiosit; lactosit; *Lacty.*

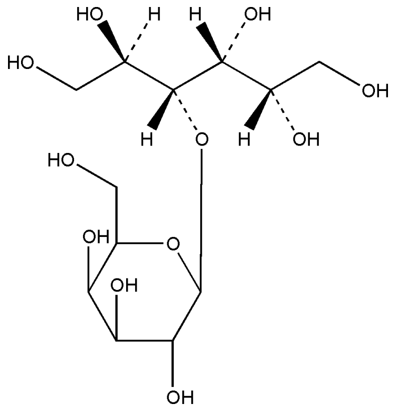
3 Chemical Name and CAS Registry Number

4-O-(β-D-Galactopyranosyl)-D-glucitol [585-86-4]
4-O-(β-D-Galactopyranosyl)-D-glucitol monohydrate [81025-04-9]
4-O-(β-D-Galactopyranosyl)-D-glucitol dihydrate [81025-03-8]

4 Empirical Formula and Molecular Weight

$C_{12}H_{24}O_{11}$	344.32 (anhydrous)
$C_{12}H_{24}O_{11}\cdot H_2O$	362.34 (monohydrate)
$C_{12}H_{24}O_{11}\cdot 2H_2O$	380.35 (dihydrate)

5 Structural Formula



6 Functional Category

Sweetening agent; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Lactitol is used as a noncariogenic replacement for sucrose. It is also used as a diluent in solid dosage forms.(1) A direct-compression form is available,(2,3) as is a direct-compression blend of lactose and lactitol. Lactitol is also used therapeutically in the treatment of hepatic encephalopathy and as a laxative; *see* Section 14.

8 Description

Lactitol occurs as white orthorhombic crystals. It is odorless with a sweet taste that imparts a cooling sensation. It is available in powdered form and in a range of crystal sizes. The directly compressible form is a water-granulated product of microcrystalline aggregates.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for lactitol.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Acidity or alkalinity	+	—
Specific optical rotation	+13.5° to +15.5°	—
Related substances	⩽1.0%	⩽1.5%
Reducing sugars	⩽0.2%	⩽0.2% as dextrose
Lead	⩽0.5 ppm	—
Nickel	⩽1 ppm	—
Water		
monohydrate	4.5–5.5%	4.5–5.5%
dihydrate	—	9.5–10.5%
anhydrous	—	⩽0.5%
Microbial contamination	⩽10^3/g	—
Residue on ignition	⩽0.1%	⩽0.5%
Heavy metals	—	⩽5 μg/g
Organic volatile impurities	—	+
Assay	96.5–102.0%	98.0–101.0%

10 Typical Properties

Acidity–alkalinity: pH = 4.5–7.0 (10% w/v solution).
Density: 1.54 g/cm^3
Heat of solution: −54 J/g
Loss of water of crystallization: 145–185°C
Moisture content: 4.5–5.5% for the monohydrate; ⩽0.5% for the anhydrous.
Osmolarity: a 7% w/v aqueous solution is isoosmotic with serum.
Refractive index:
n_D^{20} = 1.3485 (10% solution);
n_D^{20} = 1.3650 (20% solution);
n_D^{20} = 1.3827 (30% solution);
n_D^{20} = 1.4018 (40% solution);
n_D^{20} = 1.4228 (50% solution);
n_D^{20} = 1.4466 (60% solution).
Solubility: slightly soluble in ethanol (95%) and ether. Soluble 1 in 1.75 of water at 20°C; 1 in 1.61 at 30°C; 1 in 1.49 at 40°C; 1 in 1.39 at 50°C.
Specific rotation $[\alpha]_D^{20}$: +14.5° to +15°
Viscosity (dynamic):
1.3 mPa s (1.3 cP) for 10% solution at 20°C;
1.9 mPa s (1.9 cP) for 20% solution at 20°C;

3.4 mPa s (3.4 cP) for 30% solution at 20°C;
6.9 mPa s (6.9 cP) for 40% solution at 20°C;
18.9 mPa s (18.9 cP) for 50% solution at 20°C;
80.0 mPa s (80.0 cP) for 60% solution at 20°C.

11 Stability and Storage Conditions

Lactitol as the monohydrate is nonhygroscopic and is stable under humid conditions. It is stable to heat and does not take part in the Maillard reaction. In acidic solution, lactitol slowly hydrolyzes to sorbitol and galactose. Lactitol is very resistant to microbiological breakdown and fermentation. Store in a well-closed container. When the compound is stored in an unopened container at 25°C and 60% relative humidity, a shelf-life in excess of 3 years is appropriate.

12 Incompatibilities

—

13 Method of Manufacture

Lactitol is produced by the catalytic hydrogenation of lactose.

14 Safety

Lactitol is regarded as a nontoxic and nonirritant substance. It is not fermented significantly in the mouth, and is not cariogenic.(4) It is not absorbed in the small intestine, but is broken down by microflora in the large intestine,(5) and is metabolized independently of insulin. In large doses it has a laxative effect; therapeutically, 10–20 g daily in a single oral dose is administered for this purpose.

LD_{50} (mouse, oral): >23 g/kg(6)
LD_{50} (rat, oral): 30 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe.

17 Related Substances

—

18 Comments

Finlac DC is a commercially available water-granulated directly compressible lactitol.(2)

Lactitol has a sweetening power about one-third that of sucrose. It does not promote dental caries and has a caloric value of 9.9 J/g (2.4 cal/g).

The EINECS number for lactitol is 209-566-5.

19 Specific References

1 Allen LV. Featured excipient: capsule and tablet diluents. *Int J Pharm Compound* 2000; **4**(4): 306–310, 324–325.
2 Armstrong NA. Direct compression characteristics of lactitol. *Pharm Technol Eur* 1998; **10**(2): 42–46.
3 Muzikova J. A study of compressibility of directly compacting forms of lactitol. *Ceska Slov Form* 2003; **52**(5): 241–243.
4 Grenby TH, Philips A, Mistry M. Studies on the dental properties of lactitol compared with five other bulk sweeteners *in vitro*. *Caries Res* 1989; **23**: 315–319.
5 Grimble GK, Patil DH, Silk DBA. Assimilation of lactitol, an unabsorbed disaccharide in the normal human colon. *Gut* 1988; **29**: 1666–1671.
6 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 2198.

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Armstrong NA. Tablet manufacture. In: Swarbrick J, Boylan JC, eds. *Encyclopedia of Pharmaceutical Technology*, 2nd edn, vol. **3**. New York: Marcel Dekker, 2002: 2713–2732.
van Uyl CH. Technical and commercial aspects of the use of lactitol in foods as a reduced-calorie bulk sweetener. *Dev Sweeteners* 1987; **3**: 65–81.
van Velthuijsen JA. Food additives derived from lactose: lactitol and lactitol palmitate. *J Agric Food Chem* 1979; **27**: 680–686.

21 Authors

NA Armstrong.

22 Date of Revision

16 August 2005.

Lactose, Anhydrous

1 Nonproprietary Names

BP: Anhydrous lactose
JP: Anhydrous lactose
PhEur: Lactosum anhydricum
USPNF: Anhydrous lactose

2 Synonyms

Anhydrous Lactose NF 60M; *Anhydrous Lactose NF Direct Tableting*; *Lactopress Anhydrous*; lactosum; lattioso; milk sugar; *Pharmatose DCL 21*; *Pharmatose DCL 22*; saccharum lactis; *Super-Tab Anhydrous*.

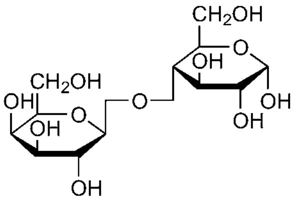
3 Chemical Name and CAS Registry Number

O-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose [63-42-3]

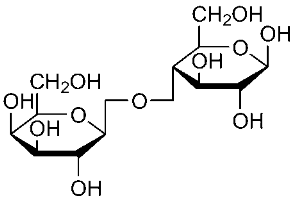
4 Empirical Formula and Molecular Weight

$C_{12}H_{22}O_{11}$ 342.30

5 Structural Formula



Anhydrous α-lactose



Anhydrous β-lactose

The PhEur 2005 describes anhydrous lactose as O-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose; or a mixture of O-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose and O-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose. The USPNF 23 describes anhydrous lactose as being primarily β-lactose or a mixture of α- and β-lactose. The JP 2001 describes anhydrous lactose as β-lactose or a mixture of β-lactose and α-lactose.

6 Functional Category

Binding agent; directly compressible tableting excipient; lyophilization aid; tablet and capsule filler.

7 Applications in Pharmaceutical Formulation or Technology

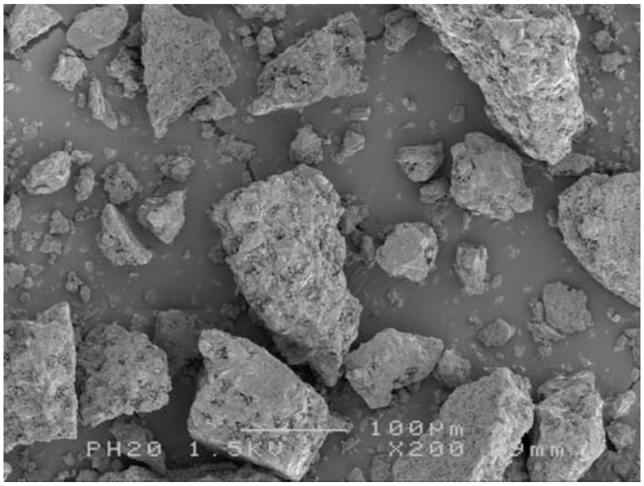
Anhydrous lactose is widely used in direct compression tableting applications and as a tablet and capsule filler and binder. Anhydrous lactose can be used with moisture-sensitive drugs due to its low moisture content.

See also Lactose, Monohydrate; Lactose, Spray-Dried.

8 Description

Lactose occurs as white to off-white crystalline particles or powder. Several different brands of anhydrous lactose are commercially available which contain anhydrous β-lactose and anhydrous α-lactose. Anhydrous lactose typically contains 70–80% anhydrous β-lactose and 20–30% anhydrous α-lactose.

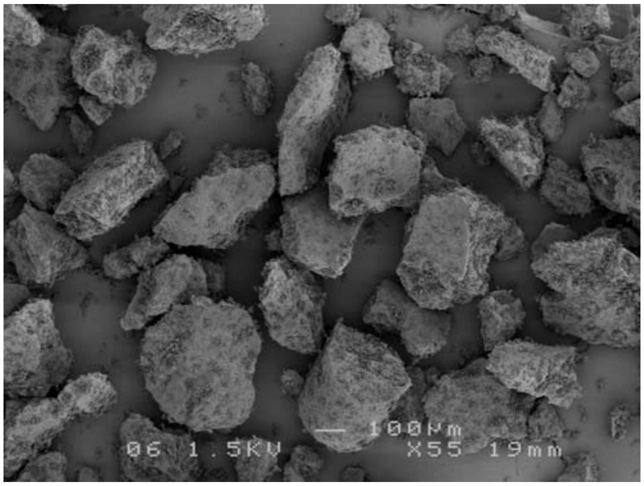
SEM: 1
Excipient: Pharmatose DCL 21
Manufacturer: DMV International
Magnification: 200×
Voltage: 1.5 kV



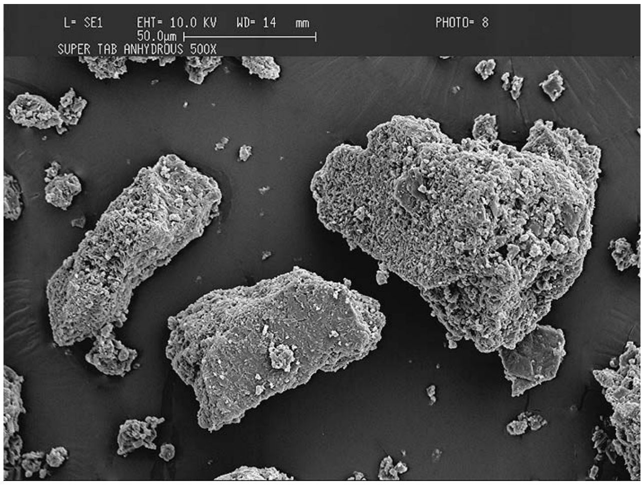
9 Pharmacopeial Specifications

See Table I.

SEM: 2
Excipient: Pharmatose DCL 22
Manufacturer: DMV International
Magnification: 55×
Voltage: 1.5 kV



SEM: 3
Excipient: Super-Tab Anhydrous
Manufacturer: New Zealand Lactose
Magnification: 500×
Voltage: 10 kV



10 Typical Properties

Angle of repose: 39° for *Pharmatose DCL 21* and 38° for *Super-Tab Anhydrous*.

Brittle fracture index: 0.0362

Bonding index: 0.0049 (at compression pressure 177.8 MPa)[a]

Density (true): 1.589 g/cm^3 for anhydrous β-lactose; 1.567 g/cm^3 for *Super-Tab Anhydrous*.

Density (bulk): 0.68 g/cm^3 for *Pharmatose DCL 21*; 0.67 g/cm^3 for *Pharmatose DCL 22*; 0.65 g/cm^3 for *Super-Tab Anhydrous*.

Density (tapped): 0.88 g/cm^3 for *Pharmatose DCL 21*; 0.79 g/cm^3 for *Pharmatose DCL 22*; 0.87 g/cm^3 for *Super-Tab Anhydrous*.

Table I: Pharmacopeial specifications for lactose anhydrous.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Appearance/color of solution	+	+	+
Characters	—	+	—
Optical rotation	+54.4 to +55.9°	+54.4 to +55.9°	+54.4 to +55.9°
Acidity or alkalinity	+	+	+
Heavy metals	⩽5 ppm	⩽5 ppm	⩽5 μg/g
Absorbance			
210–220 nm	⩽0.25	⩽0.25	⩽0.25
270–300 nm	⩽0.07	⩽0.07	⩽0.07
Loss on drying	⩽0.5%	+[a]	⩽0.5%
Water	⩽1.0%	⩽1.0%	⩽1.0%
Residue on ignition	⩽0.1%	—	⩽0.1%
Sulfated ash	—	⩽0.1%	—
Microbial limit			
Aerobic bacteria	⩽100/g	⩽10^2/g	⩽100/g
Fungi and yeast	⩽50/g	—	⩽50/g
Escherichia coli	+	+	+
Salmonella	+	—	—
Isomer ratio	+	+[a]	+

[a] Not a mandatory test.

Melting point:
223.0°C for anhydrous α-lactose;
252.2°C for anhydrous β-lactose;
232.0°C (typical) for commercial anhydrous lactose.

Particle size distribution: *see* Table II.

Permanent deformation pressure: 521.0 MPa (at compression pressure 177.8 MPa)[a]

Reduced modulus of elasticity: 5315 (at compression pressure 177.8 MPa)[a]

Solubility: soluble in water; sparingly soluble in ethanol (95%) and ether.

Specific surface area: 0.41 m^2/g for *Pharmatose DCL 22*; 0.37 m^2/g for *Super-Tab Anhydrous*.

Specific rotation $[\alpha]_D^{25}$ **:** 54.4° to 55.9°

Tensile strength: 2.577 MPa (at compression pressure 177.8 MPa)[a]

Water content: ⩽0.5% loss on drying and ⩽1.0% water content for *Anhydrous Lactose NF Direct Tableting* and *Anhydrous Lactose NF 60M*; 0.2% loss on drying and 0.5% water content for *Pharmatose DCL 21* (typical); 0.2% loss on drying and 0.2% water content for *Pharmatose DCL 22* (typical); 0.15% loss on drying for *Super-Tab Anhydrous* (typical).

[a] Methods for characterizing the mechanical properties of compacts of pharmaceutical ingredients are specified in the *Handbook of Pharmaceutical Excipients*, 3rd edn.(1)

11 Stability and Storage Conditions

Mold growth may occur under humid conditions (80% RH and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions; *see* Section 12. At 80°C and 80% RH, tablets containing anhydrous lactose have been shown to expand 1.2 times after one day.(2)

Lactose anhydrous should be stored in a well-closed container in a cool, dry place.

Table II: Particle size distribution of selected commercially available lactoses.

Supplier/grade	Percentage less than stated size				
	<45 μm	<53 μm	<75 μm	<150 μm	<250 μm
Borculo Domo Ingredients					
Lactopress Anhydrous	—	⩽30	—	—	⩾80
Lactopress Anhydrous 250	⩽20	—	—	40–65	⩾80
DMV International					
Pharmatose DCL 21	15	—	—	50	85
Pharmatose DCL 22	5	—	—	35	75
Quest International Inc. (Sheffield Products)					
Anhydrous Lactose NF Direct Tableting	—	—	20–30	35–68	80–90
Anhydrous Lactose NF 60M	—	—	10–40	45–83	95–100
Lactose New Zealand					
Super-Tab Anhydrous	—	—	16	39	69

12 Incompatibilities

Lactose anhydrous is incompatible with strong oxidizers. When mixtures containing a hydrophobic leukotriene antagonist and anhydrous lactose or lactose monohydrate were stored for six weeks at 40°C and 75% RH, the mixture containing anhydrous lactose showed greater moisture uptake and drug degradation.(3)

Studies have also shown that in blends of roxifiban acetate (DMP-754) and lactose anhydrous, the presence of lactose anhydrous accelerated the hydrolysis of the ester and amidine groups.(4)

See Lactose, Monohydrate.

13 Method of Manufacture

There are two anhydrous forms of lactose: α-lactose and β-lactose. The anhydrous forms that are commercially available may exhibit hygroscopicity at high relative humidities. Anhydrous lactose is produced by roller drying a solution of lactose above 93.5°C. The resulting product is then milled and sieved. Two anhydrous α-lactoses can be prepared using special drying techniques: one is unstable and hygroscopic, the other exhibits good compaction properties.(5) However, these materials are not commercially available.

14 Safety

Lactose is widely used in pharmaceutical formulations as a diluent and filler-binder in oral capsule and tablet formulations. It may also be used in intravenous injections. Adverse reactions to lactose are largely due to lactose intolerance, which occurs in individuals with a deficiency of the intestinal enzyme lactase, and is associated with oral ingestion of amounts well over those in solid dosage forms.

See Lactose, Monohydrate.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of materials handled. Excessive generation of dust, or inhalation of dust, should be avoided.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IM, IV, and SC injections; oral capsules and tablets; inhalation preparations; rectal, transdermal, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Lactose, monohydrate; lactose, spray-dried.

18 Comments

Lactose anhydrous has been used experimentally in hydrophilic matrix tablet formulations(6) and evaluated for dry powder inhalation applications.(7,8) Partial hydration of anhydrous lactose increases the specific surface area and reduces the flow properties of powders but has no effect on compactibility.(9) A specification for lactose is included in the Food Chemicals Codex (FCC); *see* Lactose, Monohydrate. The EINECS number for lactose anhydrous is 200-559-2.

19 Specific References

1 Kibbe AH, ed. *Handbook of Pharmaceutical Excipients*, 3rd edn. London and Washington, DC: Pharmaceutical Press and American Pharmaceutical Association, 2000: 642–643.

2 Du J, Hoag SW. The influence of excipients on the moisture senstitive drugs aspirin and niacinamide: comparison of tablets containing lactose monohydrate with tablets containing anhydrous lactose. *Pharm Dev Tech* 2001; **6**(2): 159–166.

3 Jain R, Railkar AS, Malick AW, *et al.* Stability of a hydrophobic drug in presence of hydrous and anhydrous lactose. *Eur J Pharm Biopharm*; 1998; **46**(2): 177–182.

4 Badawy SI, Williams RC, Gilbert DC. Effect of different acids on solid state stability of an ester prodrug of a IIb/IIIa glycoprotein receptor antagonist. *Pharm Dev Technol* 1999; **4**(3): 325–331.

5 Lerk CF, Andreae AC, de Boer AH, *et al.* Increased binding capacity and flowability of alpha-lactose monohydrate after dehydration. *J Pharm Pharmacol* 1983; **35**(11): 747–748.

6 Heng PW, Chan LW, Easterbrook MG, Li X. Investigation of the influence of mean HPMC particle size and number of polymer particles on the release of aspirin from swellable hydrophilic matrix tablets. *J Control Release* 2001; **76**(1–2): 39–49.

7 Larhrib H, Zeng XM, Martin GP, *et al.* The use of different grades of lactose as a carrier for aerosolized salbutamol sulphate. *Int J Pharm* 1999; **191**(1): 1–14.

8 Vanderbist F, Wery B, Moyano-Pavon I, Moes AJ. Optimization of a dry powder inhaler formulation of nacystelyn, a new mucoactive agent. *J Pharm Pharmacol* 1999; **51**(11): 1229–1234.

9 Cal S, Iglesias G, Souto C, *et al*. Effects of hydration on the properties of a roller-dried β-lactose for direct compression. *Int J Pharm* 1996; **129**: 253–261.

20 General References

Bolhuis GK, Chowhan ZT. Materials for direct compaction. In: Alderborn G, Nystrom C, eds. *Pharmaceutical Powder Compaction Technology.* New York: Marcel Dekker, 1996: 469–473.

Borculo Domo Ingredients. Technical literature: *Lactopress Anhydrous*, *Lactopress Anhydrous 250*, 2003.

DMV International. Technical literature: *Pharmatose DCL 21*, 2003.

DMV International. Technical literature: *Pharmatose DCL 22*, 2004.

Lactose New Zealand. Technical literature: *Super-Tab Anhydrous*, 2004.

Quest International Inc. (Sheffield Products). Technical literature: *Anhydrous Lactose NF Direct Tableting*, *Anhydrous Lactose NF 60M*, 2004.

21 Authors

S Edge, A Kibbe, K Kussendrager.

22 Date of Revision

27 August 2005.

Lactose, Monohydrate

1 Nonproprietary Names

BP: Lactose monohydrate
PhEur: Lactosum monohydricum
JP: Lactose
USPNF: Lactose monohydrate

2 Synonyms

See Tables II and III.

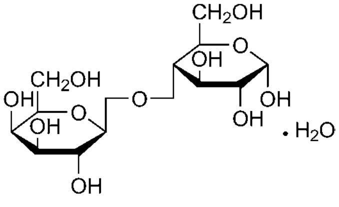
3 Chemical Name and CAS Registry Number

O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate [64044-51-5]

4 Empirical Formula and Molecular Weight

$C_{12}H_{22}O_{11}\cdot H_2O$ 360.31

5 Structural Formula



α-Lactose monohydrate

The USPNF 23 describes lactose monohydrate as a natural disaccharide, obtained from milk, which consists of one galactose and one glucose moiety. The PhEur 2005 describes lactose monohydrate as the monohydrate of O-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose. It is stated in the USPNF 23 that lactose monohydrate may be modified as to its physical characteristics, and may contain varying proportions of amorphous lactose.

6 Functional Category

Binding agent; diluent for dry-powder inhalers; tablet binder; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Lactose is widely used as a filler or diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas.(1–13) Lactose is also used as a diluent in dry-powder inhalation.(14–16) Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics. This permits the selection of the most suitable material for a particular application; for example, the particle size range selected for capsules is often dependent on the type of encapsulating machine used. Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size permits better mixing with other formulation ingredients and utilizes the binder more efficiently.

Other applications of lactose include use in lyophilized products, where lactose is added to freeze-dried solutions to increase plug size and aid cohesion. Lactose is also used in combination with sucrose (approximately 1 : 3) to prepare sugar-coating solutions.

Direct-compression grades of lactose monohydrate are available as granulated/agglomerated α-lactose monohydrate, containing small amounts of anhydrous lactose.

Direct-compression grades are often used to carry lower quantities of drug and this permits tablets to be made without granulation.

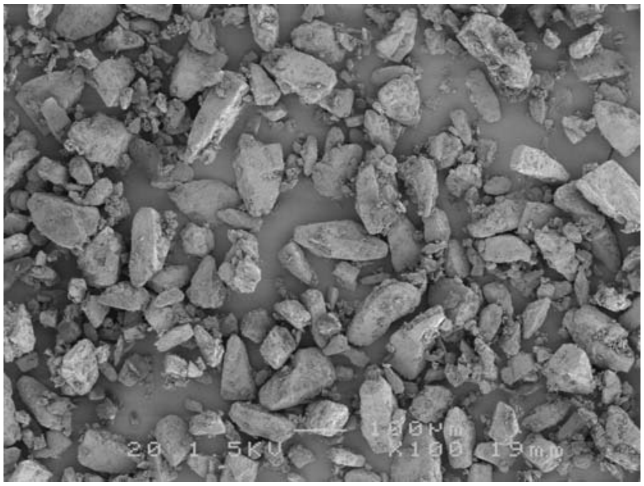
Other directly compressible lactoses are spray-dried lactose and anhydrous lactose. *See* Lactose, Spray-Dried, Lactose, Anhydrous.

8 Description

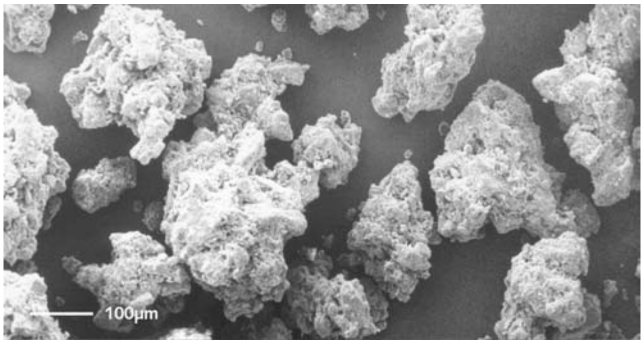
In the solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e. α-lactose monohydrate, β-lactose anhydrous, and α-lactose anhydrous. The stable crystalline forms of lactose are α-lactose monohydrate, β-lactose anhydrous, and stable α-lactose anhydrous.

Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; α-lactose is approximately 20% as sweet as sucrose, while β-lactose is 40% as sweet.

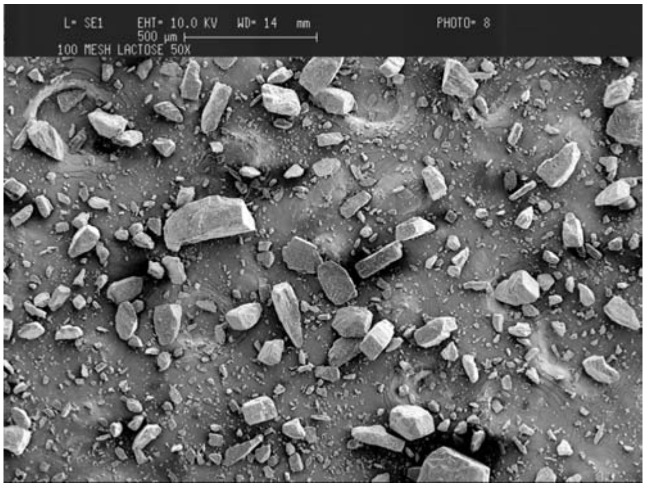
SEM: 1
Excipient: Pharmatose 125M
Manufacturer: DMV International
Magnification: 100×
Voltage: 1.5 kV



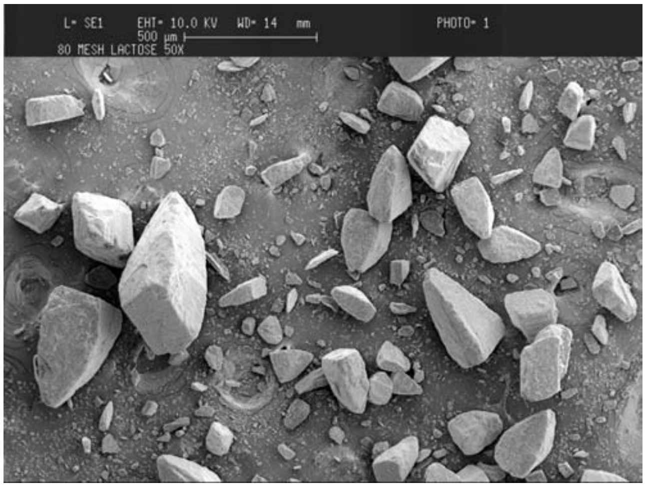
SEM: 2
Excipient: Pharmatose DCL 15
Manufacturer: DMV International



SEM: 3
Excipient: Wyndale Milled 100 Mesh
Manufacturer: Lactose New Zealand
Magnification: 50×
Voltage: 10 kV



SEM: 4
Excipient: Wyndale Sieved 80 Mesh
Manufacturer: Lactose New Zealand
Magnification: 50×
Voltage: 10 kV



9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for lactose, monohydrate.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	+	+	—
Appearance of solution	+	+	+
Acidity or alkalinity	+	+	+
Specific optical rotation	+54.4 to +55.9°	+54.4 to +55.9°	+54.4 to +55.9°
Absorbance			
at 210–220 nm	⩽0.25	⩽0.25	⩽0.25
at 270–300 nm	⩽0.07	⩽0.07	⩽0.07
Heavy metals	⩽5 ppm	⩽5 ppm	⩽5 μg/g
Water	4.5–5.5%[a]	4.5–5.5%	4.5–5.5%
Sulfated ash	⩽0.1%	⩽0.1%	—
Microbial limit			
Aerobic bacteria	⩽100/g	⩽10^2/g	⩽100/g
Fungi and yeast	⩽50/g	—	⩽50/g
Escherichia coli	+	+	+
Salmonella	+	—	—
Residue on ignition	—	—	⩽0.1%
Loss on drying	⩽0.5%[b]	—	⩽0.5%[c]

[a] 4.0–5.5% for granulated powder.

[b] For the granulated powder, not more than 1.0%.

[c] Modified monohydrate form, not more than 1.0%.

10 Typical Properties

Angle of repose: 33° for *Pharmatose DCL 15*; 32° for *Tablettose 70* and *Tablettose 80.*

Brittle fracture index:
0.0749 (at compression pressure 189.5 MPa);
0.0883 (at compression pressure 191.0 MPa).[(a)]

Bonding index:
0.0081 (at compression pressure 189.5 MPa);
0.0052 (at compression pressure 191.0 MPa).[(a)]

Compression pressure: 18.95–19.10 kN/cm^2

Density (true): 1.545 g/cm^3 (α-lactose monohydrate)

Density (bulk): *see* Table II.

Density (tapped): *see* Table II.

Melting point: 201–202°C (for dehydrated α-lactose monohydrate)

Moisture content: lactose monohydrate contains approximately 5% w/w water of crystallization and normally has a range of 4.5–5.5% w/w water content. *See* Table II.

Particle size distribution: *see* Table III.

Permanent deformation pressure:
370.0 MPa (at compression pressure 189.5 MPa);
485.0 MPa (at compression pressure 191.0 MPa).[(a)]

Reduced modulus of elasticity:
1472 (at compression pressure 189.5 MPa);
5155 (at compression pressure 191.0 MPas).[(a)]

Solubility: *see* Table IV.

Specific surface area: 0.08–0.14 m^2/g for *Lactochem Crystals* and *Lactochem Lactohale*;[(14)] 0.23 m^2/g for *Pharmatose 200M.*

Specific rotation $[\alpha]_D^{20}$: +54.4° to +55.9° as a 10% w/v solution. Lactose exhibits mutarotation and an equilibrium

Table II: Typical physical properties of selected commercially available lactose, monohydrate.

Supplier/grade	Density (bulk) (g/cm^3)	Density (tapped) (g/cm^3)	Water content (%)
Borculo Domo Ingredients			
Lactochem Coarse Crystals	0.75	0.88	—
Lactochem Crystals	0.74	0.86	—
Lactochem Fine Crystals	0.73	0.85	—
Lactochem Extra Fine Crystals	0.73	0.86	—
Lactochem Coarse Powder	0.71	0.95	—
Lactochem Regular Powder	0.62	0.92	—
Lactochem Powder	0.64	0.89	—
Lactochem Fine Powder	0.61	0.84	—
Lactochem Extra Fine Powder	0.45	0.74	—
Lactochem Super Fine Powder	0.47	0.74	—
DMV International			
Pharmatose DCL 15	0.50	0.64	4.8
Pharmatose 50M	0.71	0.83	5.2
Pharmatose 80M	0.76	0.91	5.2
Pharmatose 90M	0.74	0.89	5.2
Pharmatose 100M	0.73	0.88	5.2
Pharmatose 110M	0.73	0.89	5.2
Pharmatose 125M	0.67	0.86	5.2
Pharmatose 150M	0.60	0.88	5.2
Pharmatose 200M	0.56	0.84	5.2
Pharmatose 350M	0.51	0.80	5.2
Pharmatose 450M	0.48	0.75	5.2
HMS Coarse Powder	0.77	0.95	5.2
HMS Extrafine Crystal	0.75	0.90	5.2
HMS Regular Grade Fine Powder	0.64	0.89	5.2
HMS Impalpable	0.58	0.85	5.2
Foremost Farms USA			
NF Lactose 310	0.66	0.92	4.8–5.2
NF Lactose 312	0.53	0.81	4.8–5.2
NF Lactose 313	0.44	0.72	4.8–5.2
Meggle GmbH			
CapsuLac 60	0.59	0.70	5.2
GranuLac 70	0.72	0.90	5.2
GranuLac 140	0.66	0.89	5.2
GranuLac 200	0.54	0.80	5.2
GranuLac 230	0.47	0.76	5.2
PrismaLac 40	0.47	0.54	5.2
SacheLac 80	0.60	0.71	5.2
SorboLac 400	0.36	0.78	5.2
SpheroLac 100	0.69	0.84	5.2
Tablettose 100	0.54	0.74	5.2
Tablettose 80	0.57	0.72	5.2
Tablettose 70	0.51	0.62	—
Inhalac 70	0.60	0.66	5.2
Inhalac 120	0.68	0.78	5.2
Inhalac 230	0.69	0.80	5.2
Quest International Inc. (Sheffield Products)			
Lactose Monohydrate NF 80M	—	—	4.5–5.5
Lactose Monohydrate NF Capsulating Grade	—	—	4.5–5.5
Lactose Monohydrate NF Impalpable	—	—	4.5–5.5

mixture containing 62% β-lactose and 38% α-lactose is obtained instantly on the addition of a trace of ammonia.

Tensile strength:

2.987 MPa (at compression pressure 189.5 MPa);
2.517 MPa (at compression pressure 191.0 MPa).(a)

Water content: *see* Table II.

(a) Methods for characterizing the mechanical properties of compacts of pharmaceutical ingredients are specified in the *Handbook of Pharmaceutical Excipients*, 3rd edn.(17)

Table IV: Solubility of lactose.

Solvent	Solubility at 20°C unless otherwise stated
Chloroform	Practically insoluble
Ethanol	Practically insoluble
Ether	Practically insoluble
Water	1 in 5.24 1 in 3.05 at 40°C 1 in 2.30 at 50°C 1 in 1.71 at 60°C 1 in 0.96 at 80°C

11 Stability and Storage Conditions

Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions; *see* Section 12. The purities of different lactoses can vary and color evaluation may be important, particularly if white tablets are being formulated. The color stabilities of various lactoses also differ.

Solutions show mutorotation; *see* Section 10.

Lactose should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products.(18)

Lactose is also incompatible with amino acids, aminophylline,(19) amfetamines,(20) and lisinopril.(21)

13 Method of Manufacture

Lactose is a natural disaccharide consisting of galactose and glucose and is present in the milk of most mammals. Commercially, lactose is produced from the whey of cows' milk; whey being the residual liquid of the milk following cheese and casein production. Cows' milk contains 4.4–5.2% lactose; lactose constitutes 38% of the total solid content of milk.

α-Lactose monohydrate is prepared by crystallization from supersaturated solutions below 93.5°C. Various crystalline shapes are prism, pyramidal, and tomahawk; these are dependent on the method of precipitation and crystallization. Direct compression grades of α-lactose monohydrate are prepared by granulation/agglomeration and spray-drying.

14 Safety

Lactose is widely used in pharmaceutical formulations as a filler and filler-binder in oral capsule and tablet formulations. It may also be used in intravenous injections. Adverse reactions to

Table III: Particle size distribution of selected commercially available lactose, monohydrate.

Supplier/grade	Typical particle size distribution (%)												
	<10 μm	<32 μm	<45 μm	<63 μm	<75 μm	<100 μm	<150 μm	<200 μm	<250 μm	<315 μm	<400 μm	<600 μm	<800 μm
Borculo Domo Ingredients													
Lactochem Coarse Crystals	—	—	—	—	—	—	30–80	—	>65	—	>90(a)	—	—
Lactochem Crystals	—	—	—	—	5–30	—	55–95	—	>90	—	—	—	—
Lactochem Fine Crystals	—	—	—	—	<30	—	—	—	>90	—	—	—	—
Lactochem Extra Fine Crystal	—	—	—	—	10–45	—	—	—	>99	—	—	—	—
Lactochem Coarse Powder	—	—	—	—	40–70	—	<75	—	>95	—	—	—	—
Lactochem Powder	—	—	—	—	65–80	>85(b)	>95	—	—	—	—	—	—
Lactochem Fine Powder	—	—	—	—	>80	—	>98	—	—	—	—	—	—
Lactochem Super Fine Powder	—	—	>95	—	—	—	—	—	—	—	—	—	—
Lactochem Microfine	90	—	—	—	—	—	—	—	—	—	—	—	—
DMV International													
Pharmatose DCL15	—	—	—	—	25	—	60	—	—	—	—	—	—
Pharmatose 50M	—	—	—	—	—	—	—	<20	—	—	>80	—	—
Pharmatose 80M	—	—	—	—	—	<20	—	—	70–90	>95	—	—	—
Pharmatose 90M	—	—	—	<15	—	15–30	55–95	—	—	100	—	—	—
Pharmatose 100M	—	—	—	<15	—	—	60–80	—	>99	—	—	—	—
Pharmatose 110M	—	—	—	<20	—	30–60	75–90	—	—	100	—	—	—
Pharmatose 125M	—	—	<40	40–70	—	>90	97–100	—	—	—	—	—	—
Pharmatose 150M	—	—	<50	—	—	>70	>85	—	—	100	—	—	—
Pharmatose 200M	—	—	50–65	—	—	>90	>69	—	99–100	—	—	—	—
Pharmatose 350M	—	—	>60	—	—	>69	—	—	100	—	—	—	—
Pharmatose 450M	—	—	>90	>98	—	—	100	—	—	—	—	—	—
HMS Coarse Powder	—	—	10	—	—	30	—	—	—	—	—	—	—
HMS Extrafine Crystals	—	—	—	—	17	—	70	—	99	—	—	—	—
HMS Regular Grade Fine Powder	—	—	45	—	—	—	90	—	—	100	—	—	—
HMS Impalpable	—	—	55	—	—	87	—	—	99.7	—	—	—	—
Foremost Farms USA													
NF Lactose 310	—	—	—	—	24–50	—	—	—	—	—	—	—	—
NF Lactose 312	—	—	64–80	—	94–100	—	—	—	—	—	—	—	—
NF Lactose 313	—	—	91–98	—	99–100	—	—	—	—	—	—	—	—
Meggle GmbH													
CapsuLac 60	—	—	—	—	—	5	15	—	60	—	99	—	—
GranuLac 70	—	—	—	—	—	50	—	—	—	—	99.5	—	—
GranuLac 140	—	30	—	—	—	90	100	—	—	—	—	—	—
GranuLac 200	—	55	—	—	—	96	—	—	—	—	—	—	—
GranuLac 230	—	75	—	96	—	99.5	—	—	—	—	—	—	—
PrismaLac 40	—	—	—	—	—	—	—	4	—	—	—	—	100
SacheLac 80	—	—	—	—	—	5	—	—	63	—	100	—	—
SorboLac 400	—	95	—	99.5	—	—	—	—	—	—	—	—	—
SpheroLac 100	—	—	—	9	—	—	78	98	99.5	—	—	—	—
Tablettose 100	—	—	—	12	—	22	42	—	77	—	98	—	—
Tablettose 80	—	—	—	13	—	—	—	—	—	—	93	—	—
Tablettose 70	—	—	—	1	—	—	25	56	—	—	97	—	—
Inhalac 70	—	—	—	—	—	—	—	50	—	—	—	—	—

Supplier/grade	Typical particle size distribution (%)												
	<10 µm	<32 µm	<45 µm	<63 µm	<75 µm	<100 µm	<150 µm	<200 µm	<250 µm	<315 µm	<400 µm	<600 µm	<800 µm
Inhalac 120	—	—	—	—	—	—	50	90	—	—	—	—	—
Inhalac 230	—	—	—	—	—	50	—	—	—	—	—	—	—
Lactose New Zealand													
Wyndale Milled 100 Mesh	—	—	—	—	35	—	—	—	—	—	—	—	—
Wyndale Milled 150 Mesh	—	—	—	—	67	—	—	—	—	—	—	—	—
Wyndale Milled 200 Mesh	—	—	—	—	81	—	—	—	—	—	—	—	—
Wyndale Milled 300 Mesh	—	—	—	—	89	—	—	—	—	—	—	—	—
Wyndale Milled 350 Mesh	—	—	75	—	—	—	—	—	100	—	—	—	—
Wyndale Milled 450 Mesh	—	—	88	96	—	—	—	—	—	—	—	—	—
Wyndale Sieved 40 Mesh	—	—	—	—	—	—	3	—	17	—	—	93	—
Wyndale Sieved 60 Mesh	—	—	—	—	1	—	7	—	28	—	—	100	—
Wyndale Sieved 80 Mesh	—	—	—	—	4	—	18	—	61	—	—	100	—
Wyndale Sieved 100 Mesh	—	—	—	—	10	—	74	—	100	—	—	—	—
Wyndale Sieved 125 Mesh	—	—	35	62	—	—	—	—	—	—	—	—	—
Wyndale Sieved Special Dense	—	—	—	—	9	—	38	—	74	—	—	100	—
Quest International Inc. (Sheffield Products)													
Lactose Monohydrate NF 80M	—	—	—	—	65–90	—	93–99.5	—	99.5–100	—	—	—	—
Lactose Monohydrate NF Capsulating Grade	—	—	—	—	58–70	—	92–100	—	—	—	—	—	—
Lactose Monohydrate NF Impalpable	—	—	—	—	>90	—	98.5–100	—	—	—	—	—	—

[a] <425 µm.

[b] <106 µm.

lactose are largely attributed to lactose intolerance, which occurs in individuals with a deficiency of the intestinal enzyme lactase.(22–25) This results in lactose being undigested and may lead to cramps, diarrhea, distension, and flatulence. In lactose-tolerant individuals, lactase hydrolyzes lactose in the small intestine to glucose and galactose, which are then absorbed. Lactase levels are normally high at birth, and levels decline rapidly in early childhood. Malabsorption of lactose (hypolactasia) may occur at an early age (4–8 years) and varies among different ethnic groups. Lactose is excreted unchanged when administered intravenously.

The symptoms of lactose intolerance are caused by the osmotic effect of the unabsorbed lactose, which increases water and sodium levels in the lumen. Unabsorbed lactose, upon reaching the colon, can be fermented by colonic flora, which produces gas, causing abdominal distension and discomfort. A lactose tolerance test has been developed based on the measurement of blood glucose level and the hydrogen level in the breath. However, its usefulness has been questioned as the test is based on a 50 g dose of lactose.

Approximately 10–20% of lactose-intolerant individuals, in two studies, showed clinical symptoms of intolerance after ingestion of 3–5 g of lactose.(22,23) In one of the studies,(22) 75% of the subjects had symptoms with 12 g of lactose (equivalent to 250 mL of milk). In another,(23) eight out of 13 individuals developed diarrhea after the administration of 20 g of lactose, and nine out of 13 after the administration of 25 g.

Lower doses of lactose produce fewer adverse effects, and lactose is better tolerated if taken with other foods. As a result, there is a significant population with lactose malabsorption who are still able to ingest normal amounts of lactose, such as that in milk, without the development of adverse side effects.(24)

Most adults consume about 25 g of lactose per day (500 mL of milk) without symptoms.(25,26) When symptoms appear, they are usually mild and dose-related. The dose of lactose in most pharmaceuticals seldom exceeds 2 g per day. It is unlikely that severe gastrointestinal symptoms can be attributed to the lactose in a conventional oral solid-dosage form, especially in adults who have not previously been diagnosed as severely lactose-intolerant. However, anecdotal reports of drug-induced diarrhea due to lactose intolerance have been made following administration of pharmaceutical preparations containing lactose.

It has also been suggested that lactose intolerance may have a role in irritable bowel syndrome, but this role is currently unclear.(27)

In the past, there have been concerns over the transmissible spongiform encephalopathies (TSE) contamination of animal-derived products. However, in the light of current scientific knowledge, and irrespective of geographical origin, milk and milk derivatives are reported as unlikely to present any risk of TSE contamination; TSE risk is negligible if the calf rennet is produced in accordance with regulations.(28)

LD_{50} (rat, IP): >10 g/kg
LD_{50} (rat, oral): >10 g/kg
LD_{50} (rat, SC): >5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Excessive generation of dust, or inhalation of dust, should be avoided.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IM, IV, and SC injections; oral capsules and tablets; inhalation preparations; rectal, transdermal, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Lactose, anhydrous; lactose, spray-dried.

18 Comments

A number of different grades of lactose are commercially available that vary in their physical properties and many studies have been reported in the literature comparing the behavior of these various materials in different formulations.(6,9–11) A number of co-processed excipients which contain lactose are available for direct-compression applications: co-processed lactose and starch (*Starlac*, Meggle/Roquette Fréres),(29) lactose and microcrystalline cellulose (*Microcelac*, Meggle);(30) lactose and cellulose powder (*Cellactose*, Meggle),(31,32) lactose, povidone, and crospovidone (*Ludipress*, BASF).

Lactose may exhibit complex thermoanalytical transitions because of its several crystalline, as well as amorphous, forms. Differential scanning calorimetry (DSC) can be used effectively to characterize the composition.(33–35) For example, α-lactose becomes anhydrous at approximately 120°C. α-Lactose monohydrate may also contain a small quantity of the β-form.

The CAS number for lactose monohydrate, cycloic form is [10039-26-6]; and the CAS number for lactose monohydrate, open form is [64044-51-5]. A specification for lactose is included in the Food Chemicals Codex (FCC).

The EINECS number for lactose is 200-559-2.

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S Edge, A Kibbe, K Kussendrager.

22 Date of Revision

28 August 2005.

Lactose, Spray-Dried

1 Nonproprietary Names

None adopted.

2 Synonyms

FlowLac 100; *Lactopress Spray-Dried*; *NF Lactose–316 Fast Flo*; *NF Lactose–315*; *Pharmatose DCL 11*; *Pharmatose DCL 14*; *Super-Tab Spray-Dried*.

3 Chemical Name and CAS Registry Number

Spray-dried lactose is a mixture of amorphous lactose, which is a 1 : 1 mixture of α-and-β-lactose, and *O*-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate [64044-51-5].

4 Empirical Formula and Molecular Weight

$C_{12}H_{22}O_{11}$	342.30 (for amorphous)
$C_{12}H_{22}O_{11}\cdot H_2O$	360.31 (for monohydrate)

5 Structural Formula

See Lactose, Anhydrous and Lactose, Monohydrate.

6 Functional Category

Binding agent; directly compressible tablet excipient; tablet and capsule diluent; tablet and capsule filler.

7 Applications in Pharmaceutical Formulation or Technology

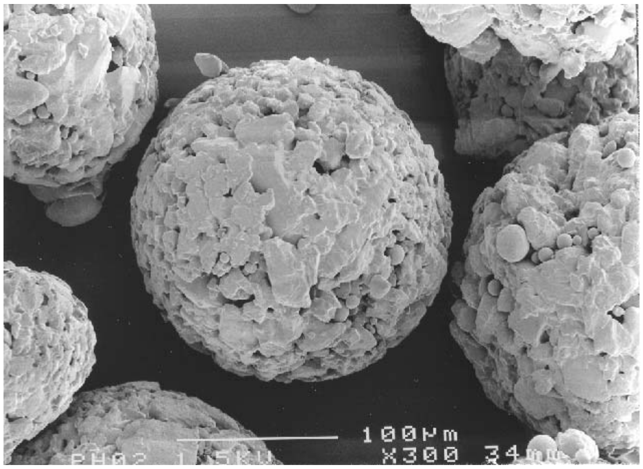
Spray-dried lactose is widely used as a binder, filler-binder, and flow aid in direct compression tableting.

See also Lactose, Monohydrate; Lactose, Anhydrous.

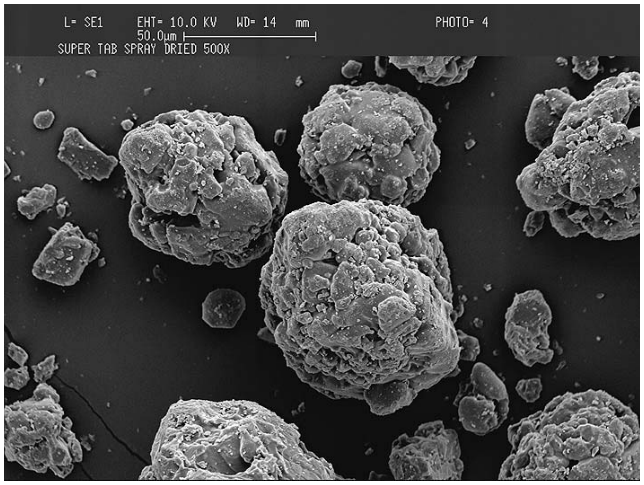
8 Description

Lactose occurs as white to off-white crystalline particles or powder. It is odorless and slightly sweet-tasting. Spray-dried direct-compression grades of lactose are generally composed of 80–90% specially prepared pure α-lactose monohydrate along with 10–20% of amorphous lactose.

SEM: 1
Excipient: Pharmatose DC 11
Manufacturer: DMV International
Magnification: 300×
Voltage: 5 kV



SEM: 2
Excipient: Super-Tab Spray-Dried
Manufacturer: Lactose New Zealand
Magnification: 500×
Voltage: 10 kV


L= SE1 EHT= 10.0 KV WD= 14 mm PHOTO= 4
50.0μm
SUPER TAB SPRAY DRIED 500X

9 Pharmacopeial Specifications

See Section 18.

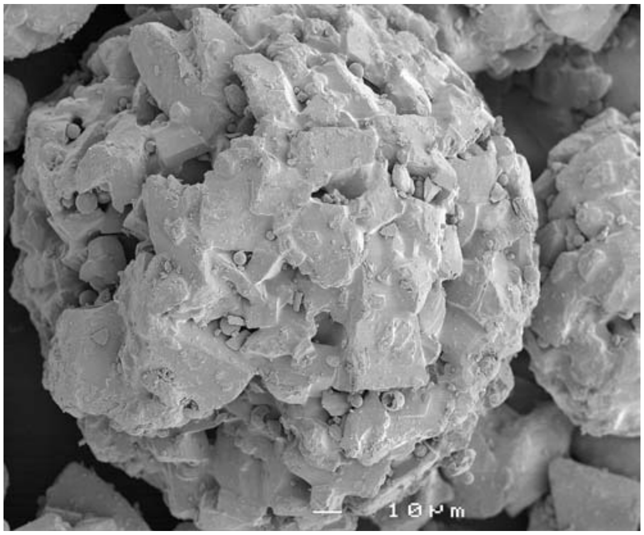
10 Typical Properties

Angle of repose: *see* Table I.
Bonding index: 0.0044 for *NF Lactose–315* (compression pressure 54.90 MPa)(a)

Table I: Typical physical properties of selected commercially available spray-dried lactose.

Supplier/grade	Angle of repose (°)	Density (bulk) (g/cm^3)	Density (tapped) (g/cm^3)	Water content (%)
Borculo Domo Ingredients				
Lactopress Spray-Dried	—	—	—	—
Lactopress Spray-Dried 250	—	—	—	—
DMV International				
Pharmatose DCL 11	30	0.61	0.73	5.0
Pharmatose DCL 14	29	0.61	0.72	5.0
Foremost Farms				
NF Lactose–316 Fast-Flo	—	0.58	0.67	4.8–5.2
NF Lactose–315	—	0.67	0.78	4.8–5.2
Meggle GmbH				
FlowLac 100	28	0.62	0.73	5.0–5.2
Lactose New Zealand				
Super-Tab Spray-Dried	31	0.62	0.79	—

SEM: 3
Excipient: Lactopress Spray-Dried
Manufacturer: Borculo Domo



Brittle fracture index: 0.1671 for *NF Lactose–315* (compression pressure 54.90 MPa)[(a)]
Density bulk: *see* Table I.
Reduced modulus of elasticity: 5648 for *NF Lactose–315* (compression pressure 5.49–54.90 MPa)[(a)]
Tensile strength: 2.368 MPa for *NF Lactose–315* (compression pressure 54.90 MPa)[(a)]
Water content: *see* Table I.

[(a)] Methods for characterizing the mechanical properties of compacts of pharmaceutical ingredients are specified in the *Handbook of Pharmaceutical Excipients*, 3rd edn.[(1)]

11 Stability and Storage Conditions

Spray-dried lactose should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

See Lactose, Anhydrous and Lactose, Monohydrate.

13 Method of Manufacture

A suspension of α-lactose monohydrate crystals in a lactose solution is atomized and dried in a spray drier.[(2,3)] Approximately 10–20% of the total amount of lactose is in solution and the remaining 80–90% is present in the crystalline form. The spray-drying process predominantly produces spherical particles. The compactibility of the material and its flow characteristics are a function of the primary particle size of the lactose monohydrate and the amount of amorphous lactose.[(4)]

14 Safety

Lactose is widely used in pharmaceutical formulations as a diluent in oral capsule and tablet formulations. It may also be used in intravenous injections.

Adverse reactions to lactose are largely due to lactose intolerance, which occurs in individuals with a deficiency of the enzyme lactase.

See Lactose, Monohydrate.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material being handled. Excessive generation of dust, or inhalation of dust, should be avoided.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IM, IV, and SC injections; oral capsules and tablets; inhalation preparations; rectal, transdermal, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK.

17 Related Substances

Lactose, anhydrous; lactose, monohydrate.

18 Comments

Spray-dried lactose was one of the first direct-compression excipients. Spray-dried lactose typically comprises lactose monohydrate and amorphous lactose (*see* Section 8); *see* Lactose, Monohydrate for the relevant pharmacopeial information.

It has been shown that during the spray-drying process the effects of nozzle orifice diameter and atomization air flow control the droplet size during atomization; however, it has also been demonstrated that increasing feed concentration results in

Table II: Particle size distribution of selected commercially available spray-dried lactose.

Supplier/grade	Percentage less than stated size					
	<32 μm	<45 μm	<75 μm	<100 μm	<150 μm	<250 μm
Borculo Domo Ingredients						
Lactopress Spray-Dried	—	⩽25	—	30–60(a)	—	⩾65
Lactopress Spray-Dried 250	—	⩽15	⩽50	30–60	—	⩾98
DMV International						
Pharmatose DCL 11	—	10	—	40	—	100
Pharmatose DCL 14	—	10	—	40	—	100
Foremost Farms						
NF Lactose–316 Fast-Flo	—	—	20–40	45–70(a)	—	99.5–100
NF Lactose–315	—	—	25–45	45–70(a)	—	—
Meggle GmbH						
FlowLac 100	6	—	—	34	—	98
Lactose New Zealand						
Super-Tab Spray-Dried	—	—	14	—	52	97

(a) <106 μm.

increased shell thickness of hollow particles that are formed.(5) The physical properties of spray-dried lactose produced from alchoholic media are directly affected by the ethanol-to-water ratio in the feed solution. Lactose spray-dried from pure ethanol was shown to be 100% crystalline, whereas lactose spray-dried from pure water was 100% amorphous. Furthermore, the surface area of the spray-dried lactose increased as a function of amorphous content.(6) Spray-dried lactoses exhibit good flow properties.(7)

Polyethylene glycol (PEG) 4000, when spray-dried with lactose, has been shown to accelerate the rate and extent of crystallization of lactose.(8) It has also been shown that spray-dried lactose composite particles containing an ion complex of chitosan are suitable for the dry-coating of tablets.(9) Spray-dried lactose and crystallized spray-dried lactose have been evaluated for dry powder inhalation.(10,11) Amorphous spray-dried lactose has also been studied in composites with PVP.(12)

See also Lactose, Anhydrous and Lactose, Monohydrate.

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S Edge, A Kibbe, K Kussendrager.

22 Date of Revision

5 August 2005.

Lanolin

1 Nonproprietary Names

BP: Wool fat
JP: Purified lanolin
PhEur: Adeps lanae
USP: Lanolin

2 Synonyms

Cera lanae; E913; lanolina; lanolin anhydrous; *Protalan anhydrous*; purified lanolin; refined wool fat.

3 Chemical Name and CAS Registry Number

Anhydrous lanolin [8006-54-0]

4 Empirical Formula and Molecular Weight

The USP 28 describes lanolin as the purified wax-like substance obtained from the wool of the sheep, *Ovis aries* Linné (Fam. Bovidae), that has been cleaned, decolorized, and deodorized. It contains not more than 0.25% w/w of water and may contain up to 0.02% w/w of a suitable antioxidant; the PhEur 2005 specifies up to 200 ppm of butylated hydroxytoluene as an antioxidant.

See also Section 18.

5 Structural Formula

See Section 4.

6 Functional Category

Emulsifying agent; ointment base.

7 Applications in Pharmaceutical Formulation or Technology

Lanolin is widely used in topical pharmaceutical formulations and cosmetics.

Lanolin may be used as a hydrophobic vehicle and in the preparation of water-in-oil creams and ointments. When mixed with suitable vegetable oils or with soft paraffin, it produces emollient creams that penetrate the skin and hence facilitate the absorption of drugs. Lanolin mixes with about twice its own weight of water, without separation, to produce stable emulsions that do not readily become rancid on storage.

See also Section 18.

8 Description

Lanolin is a pale yellow-colored, unctuous, waxy substance with a faint, characteristic odor. Melted lanolin is a clear or almost clear, yellow liquid.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for lanolin.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	—
Characters	+	+	—
Melting range	37–43°C	38–44°C	38–44°C
Acidity and alkalinity	+	—	+
Loss on drying	⩽0.5%	⩽0.5%	⩽0.25%
Residue on ignition	⩽0.1%	—	⩽0.1%
Sulfated ash	—	⩽0.15%	—
Water-soluble acids and alkalis	—	+	+
Water-soluble oxidizable substances	+	+	+
Chloride	⩽0.036%	⩽150 ppm	⩽0.035%
Ammonia	+	—	+
Acid value	⩽1.0	⩽1.0	—
Iodine value	18–36	—	18–36
Peroxide value	—	⩽20	—
Saponification value	—	90–105	—
Water absorption capacity	—	+	—
Paraffins	—	⩽1.0%	—
Petrolatum	+	—	+
Foreign substances (pesticide residues)	—	+	+
Butylated hydroxytoluene	—	⩽200 ppm	—

10 Typical Properties

Autoignition temperature: 445°C
Density: 0.932–0.945 g/cm^3 at 15°C
Flash point: 238°C
Refractive index: n_D^{40} = 1.478–1.482
Solubility: freely soluble in benzene, chloroform, ether, and petroleum spirit; sparingly soluble in cold ethanol (95%), more soluble in boiling ethanol (95%); practically insoluble in water.

11 Stability and Storage Conditions

Lanolin may gradually undergo autoxidation during storage. To inhibit this process, the inclusion of butylated hydroxytoluene is permitted as an antioxidant. Exposure to excessive or prolonged heating may cause anhydrous lanolin to darken in color and develop a strong rancidlike odor. However, lanolin may be sterilized by dry heat at 150°C. Ophthalmic ointments containing lanolin may be sterilized by filtration or by exposure to gamma irradiation.(1)

Lanolin should be stored in a well-filled, well-closed container protected from light, in a cool, dry place. Normal storage life is 2 years.

12 Incompatibilities

Lanolin may contain prooxidants, which may affect the stability of certain active drugs.

13 Method of Manufacture

Lanolin is a naturally occurring wax-like material obtained from the wool of sheep, *Ovis aries* Linné (Fam. Bovidae).

Crude lanolin is saponified with a weak alkali and the resultant saponified fat emulsion is centrifuged to remove the aqueous phase. The aqueous phase contains a soap solution from which, on standing, a layer of partially purified lanolin separates. This material is then further refined by treatment with calcium chloride, followed by fusion with unslaked lime to dehydrate the lanolin. The lanolin is finally extracted with acetone and the solvent is removed by distillation.

14 Safety

Lanolin is widely used in cosmetics and a variety of topical pharmaceutical formulations.

Although generally regarded as a nontoxic and nonirritant material, lanolin and lanolin derivatives are associated with skin hypersensitivity reactions and the use of lanolin in subjects with known sensitivity should be avoided.(2,3) Other reports suggest that 'sensitivity' arises from false positives in patch testing.(4) However, skin hypersensitivity is relatively uncommon;(5) the incidence of hypersensitivity to lanolin in the general population is estimated to be around 5 per million.(6)

Sensitivity is thought to be associated with the content of free fatty alcohols present in lanolin products rather than the total alcohol content.(7) The safety of pesticide residues in lanolin products has also been of concern.(8,9) However, highly refined 'hypoallergenic' grades of lanolin and grades with low pesticide residues are commercially available.(10) *See also* Section 18.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (ophthalmic, otic, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Cholesterol; hydrogenated lanolin; lanolin, hydrous; lanolin alcohols; modified lanolin.

See also Section 18.

Hydrogenated lanolin

Synonyms: adeps lanae hydrogenatus; hydrogenated wool fat.
Acid value: $\leqslant 1.0$
Hydroxyl value: 140–180
Melting point: 45–55°C
Saponification value: $\leqslant 8.0$
Water: $\leqslant 3.0\%$
Comments: some pharmacopeias, such as the PhEur 2005, contain a monograph for hydrogenated lanolin. This material is a mixture of higher aliphatic alcohols and sterols obtained from the direct, high-pressure, high-temperature hydrogenation of lanolin during which the esters and acids present are reduced to the corresponding alcohols. Hydrogenated lanolin may contain a suitable antioxidant; the PhEur 2005 specifies not more than 200 ppm of butylated hydroxytoluene.

Modified lanolin

Comments: some pharmacopeias, such as the USP 28, contain a monograph for modified lanolin. This material is lanolin that has been processed to reduce the contents of free lanolin alcohols and detergent and pesticide residues. It contains not more than 0.25% w/w of water. The USP 28 specifies that it may contain not more than 0.02% w/w of a suitable antioxidant.

18 Comments

Lanolin (the anhydrous material) may be confused in some instances with hydrous lanolin since the USP formerly contained monographs for 'lanolin' and 'anhydrous lanolin' in which the name 'lanolin' referred to the material containing 25–30% w/w of purified water. However, in the USP 28 the former lanolin monograph (hydrous lanolin) is deleted and the monograph for anhydrous lanolin is renamed 'lanolin'.

Since lanolin is a natural product obtained from various geographical sources, its physical characteristics such as color, consistency, iodine value, saponification value, and hydroxyl value may vary for the products from different sources. Consequently, formulations containing lanolin from different sources may also have different physical properties.

A wide range of grades of lanolin are commercially available that have been refined to different extents in order to produce hypoallergenic grades or grades with low pesticide contents.

Many lanolin derivatives are also commercially available that have properties similar to those of the parent material and include: acetylated lanolin; ethoxylated or polyoxyl lanolin (water-soluble); hydrogenated lanolin; isopropyl lanolate; lanolin oil; lanolin wax; liquid lanolin; and water-soluble lanolin.

A specification for anhydrous lanolin is contained in the Food Chemicals Codex (FCC), where it is described as being used as a masticatory substance in chewing gum base. The EINECS number for lanolin is 232-348-6.

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21 Authors

AJ Winfield.

22 Date of Revision

15 August 2005.

Lanolin Alcohols

1 Nonproprietary Names

BP: Wool alcohols
PhEur: Alcoholes adipis lanae
USPNF: Lanolin alcohols

2 Synonyms

Alcoholia lanae; alcolanum; *Argowax*; *Hartolan*; lanalcolum; *Ritawax*; wool wax alcohols.

3 Chemical Name and CAS Registry Number

Lanolin alcohols [8027-33-6]

4 Empirical Formula and Molecular Weight

Lanolin alcohols is a crude mixture of steroidal and triterpene alcohols, including not less than 30% cholesterol, and 10–13% isocholesterol. The USPNF 23 permits the inclusion of up to 0.1% w/w of a suitable antioxidant, while the PhEur 2005 specifies that lanolin alcohols may contain up to 200 ppm of butylated hydroxytoluene as an antioxidant.

5 Structural Formula

See Section 4.

6 Functional Category

Emulsifying agent; ointment base.

7 Applications in Pharmaceutical Formulation or Technology

Lanolin alcohols is used in topical pharmaceutical formulations and cosmetics as a hydrophobic vehicle with emollient properties, e.g., in preparations for dry skin and dry eyes. It is also used in the preparation of water-in-oil creams and ointments at concentrations as low as 2% w/w. The proportion of water that can be incorporated into petrolatum is increased threefold by the addition of 5% lanolin alcohols. Such emulsions do not crack upon the addition of citric, lactic, or tartaric acids.

8 Description

Lanolin alcohols is a pale yellow to golden brown-colored solid that is plastic when warm but brittle when cold. It has a faint characteristic odor. *See also* Section 4.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for lanolin alcohols.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Melting range	⩾58°C	⩾56°C
Acidity and alkalinity	+	+
Clarity of solution	+	—
Loss on drying	⩽0.5%	⩽0.5%
Residue on ignition	⩽0.1%	⩽0.15%
Copper	—	⩽5 ppm
Acid value	⩽2.0	⩽2.0
Hydroxyl value	120–180	—
Peroxide value	⩽15	—
Saponification value	⩽12	⩽12
Water absorption capacity	+	—
Butylated hydroxytoluene	⩽200 ppm	—
Content of sterols (as cholesterol)	⩾30.0%	⩾30.0%

10 Typical Properties

Solubility: freely soluble in chloroform, dichloromethane, ether, and light petroleum; soluble 1 in 25 parts of boiling ethanol (95%); slightly soluble in ethanol (90%); practically insoluble in water.

11 Stability and Storage Conditions

Lanolin alcohols may gradually undergo autoxidation during storage. Store in a well-closed, well-filled container, protected from light, in a cool, dry place. Normal storage life is approximately 2 years.

12 Incompatibilities

Incompatible with coal tar, ichthammol, phenol, and resorcinol.

13 Method of Manufacture

Lanolin alcohols is prepared by the saponification of lanolin followed by separation of the fraction containing cholesterol and other alcohols.

14 Safety

Lanolin alcohols is widely used in cosmetics and topical pharmaceutical formulations and is generally regarded as a nontoxic material. However, lanolin alcohols may be irritant to the skin and hypersensitivity can occur in some individuals.(1)

See also Lanolin.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (ophthalmic and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Cholesterol; lanolin; lanolin, hydrous; petrolatum and lanolin alcohols; mineral oils.

18 Comments

Water-in-oil emulsions prepared with lanolin alcohols, unlike those made with lanolin, do not show surface darkening, nor do they develop an objectionable odor in hot weather.

The EINECS number for lanolin alcohols is 232-430-1.

19 Specific References

1 Wakelin SH, Smith H, White IR, *et al*. A retrospective analysis of contact allergy to lanolin. *B J Dermatol* 2001; **145**(1): 28–31.

20 General References

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Khan AR, Iyer BV, Cirelli RA, Vasavada RC. *In vitro* release of salicylic acid from lanolin alcohols–ethylcellulose films. *J Pharm Sci* 1984; 73: 302–305.

Osborne DW. Phase behavior characterization of ointments containing lanolin or a lanolin substitute. *Drug Dev Ind Pharm* 1993; **19**: 1283–1302.

Smolinske SC. *Handbook of Food, Drug, and Cosmetic Excipients*. Boca Raton, FL: CRC Press, 1992: 225–229.

21 Authors

AJ Winfield.

22 Date of Revision

15 August 2005.

Lanolin, Hydrous

1 Nonproprietary Names

BP: Hydrous wool fat
JP: Hydrous lanolin
PhEur: Adeps lanae cum aqua

2 Synonyms

Lipolan.

3 Chemical Name and CAS Registry Number

Hydrous lanolin [8020-84-6]

4 Empirical Formula and Molecular Weight

The JP 2001 describes hydrous lanolin as a mixture of lanolin and 25–30% w/w purified water. The PhEur 2005 describes hydrous lanolin as a mixture of lanolin and 25% w/w purified water; *see also* Section 18. The PhEur 2005 additionally permits the inclusion of up to 150 ppm of butylated hydroxytoluene as an antioxidant.

See also Lanolin.

5 Structural Formula

See Section 4.

6 Functional Category

Emulsifying agent; ointment base.

7 Applications in Pharmaceutical Formulation or Technology

Hydrous lanolin is widely used in topical pharmaceutical formulations and cosmetics in applications similar to those for lanolin.

Hydrous lanolin is commonly used in the preparation of water-in-oil creams and ointments. More water may be incorporated into hydrous lanolin than into lanolin.

See also Section 18.

8 Description

Hydrous lanolin is a pale yellow-colored, unctuous substance with a faint characteristic odor. When melted by heating on a water bath, hydrous lanolin separates into a clear oily layer and a clear water layer.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for hydrous lanolin.

Test	JP 2001	PhEur 2005
Identification	+	+
Characters	+	+
Melting point	39°C	38–44°C
Acidity and alkalinity	+	—
Water absorption capacity	—	+
Water-soluble acids and alkalis	+	+
Water-soluble oxidizable substances	+	+
Chloride	⩽0.036%	⩽115 ppm
Ammonia	+	—
Paraffins	+	⩽1.0%
Petrolatum	+	—
Acid value	⩽1.0	⩽0.8
Peroxide value	—	⩽15
Iodine value	18–36	—
Saponification value	—	67–79
Butylated hydroxytoluene	—	⩽150 ppm
Nonvolatile matter (wool fat content)	70–75%	72.5–77.5%
Sulfated ash	—	⩽0.1%

10 Typical Properties

Solubility: practically insoluble in chloroform, ether, and water. Only the fat component of hydrous lanolin is soluble in organic solvents.

11 Stability and Storage Conditions

Hydrous lanolin should be stored in a well-filled, well-closed container protected from light, in a cool, dry place. Normal storage life is 2 years.

See also Lanolin.

12 Incompatibilities

See Lanolin.

13 Method of Manufacture

Lanolin is melted, and sufficient purified water is gradually added with constant stirring.

14 Safety

Hydrous lanolin is used in cosmetics and a number of topical pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material, although it has been associated with hypersensitivity reactions. *See* Lanolin for further information.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (ophthalmic, topical, transdermal, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Cholesterol; lanolin; lanolin alcohols.

18 Comments

Lanolin (the anhydrous material) may be confused in some instances with hydrous lanolin since the USP formerly contained monographs for 'lanolin' and 'anhydrous lanolin' in which the name 'lanolin' referred to the material containing 25–30% w/w of purified water.

19 Specific References

—

20 General References

Barnett G. Lanolin and derivatives. *Cosmet Toilet* 1986; **101**(3): 23–44.
Osborne DW. Phase behavior characterization of ointments containing lanolin or a lanolin substitute. *Drug Dev Ind Pharm* 1993; **19**: 1283–1302.
Smolinske SC. *Handbook of Food, Drug, and Cosmetic Excipients*. Boca Raton, FL: CRC Press, 1992: 225–229.

21 Authors

AJ Winfield.

22 Date of Revision

15 August 2005.

Lauric Acid

1 Nonproprietary Names

None adopted.

2 Synonyms

C-1297; dodecanoic acid; dodecoic acid; duodecylic acid; *n*-dodecanoic acid; *Hydrofol acid 1255*; *Hydrofol acid 1295*; *Hystrene 9512*; laurostearic acid; *Neo-fat 12*; *Neo-fat 12–43*; *Ninol AA62 Extra*; 1-undecanecarboxylic acid; vulvic acid; *Wecoline 1295*.

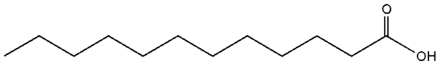
3 Chemical Name and CAS Registry Number

Dodecanoic acid [143-07-7]

4 Empirical Formula and Molecular Weight

$C_{12}H_{24}O_2$ 200.32

5 Structural Formula



6 Functional Category

Emulsifying agent; food additive; lubricant; surfactant.

7 Applications in Pharmaceutical Formulation or Technology

Lauric acid is widely used in cosmetics and food products. In pharmaceutical applications it has also been examined for use as an enhancer for topical penetration and transdermal absorption,(1–11) rectal absorption,(12,13) buccal delivery,(14) and intestinal absorption.(15,16) It is also useful for stabilizing oil-in-water emulsions.(17) Lauric acid has also been evaluated for use in aerosol formulations.(18)

8 Description

Lauric acid occurs as a white crystalline powder with a slight odor of bay oil.

9 Pharmacopeial Specifications

—

10 Typical Properties

Boiling point: 298.9°C (at 760 mmHg).
Density:
0.883 g/cm^3 at 20°C;
0.8679 g/cm^3 at 50°C.
Enthalpy of fusion: 36.3 kJ mol^{-1}
Melting point: 43.2–43.8°C
Partition coefficient: Log *P* (octanol : water) = 4.6
Refractive index:
$n_D^{82} = 1.418$;
$n_D^{70} = 1.423$;
$n_D^{45} = 1.432$.
Solubility: 4.81 mg/mL at 25°C. Very soluble in ether, ethanol (95%), and methanol; soluble in acetone; slightly soluble in chloroform; miscible with benzene.
Specific gravity: 0.9
Surface tension: 26.6 mN/m at 70°C
Vapor pressure:
10 Pa at 100°C;
100 Pa at 128°C.
Viscosity (dynamic): 7.3 mPa s at 50°C
Viscosity (kinematic): 8.41 mPa s at 50°C

11 Stability and Storage Conditions

Lauric acid is stable at normal temperatures and should be stored in a cool, dry place. Avoid sources of ignition and contact with incompatible materials.

12 Incompatibilities

Lauric acid is incompatible with strong bases, reducing agents, and oxidizing agents.

13 Method of Manufacture

Lauric acid is a fatty carboxylic acid isolated from vegetable and animal fats or oils. For example, coconut oil and palm kernel oil both contain high proportions of lauric acid. Isolation from natural fats and oils involves hydrolysis, separation of the fatty acids, hydrogenation to convert unsaturated fatty acids to saturated acids, and finally distillation of the specific fatty acid of interest.

14 Safety

Lauric acid is widely used in cosmetic preparations, in the manufacture of food-grade additives, and in pharmaceutical formulations. General exposure to lauric acid occurs through the consumption of food and through dermal contact with cosmetics, soaps, and detergent products. Lauric acid is toxic when administered intravenously.

Occupational exposure may cause local irritation of eyes, nose, throat, and respiratory tract,(19) although lauric acid is considered safe and nonirritating for use in cosmetics.(20) No toxicological effects were observed when lauric acid was administered to rats at 35% of the diet for 2 years.(21) Acute exposure tests in rabbits indicate mild irritation.(20) After subcutaneous injection into mice, lauric acid was shown to be noncarcinogenic.(22)

LD_{50} (mouse, IV): 0.13 g/kg(23,24)
LD_{50} (rat, oral): 12 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. No occupational exposure limits have been established. Under conditions of frequent use or heavy exposure, respiratory protection may be required. When heated, lauric acid emits an acrid smoke and irritating fumes; therefore, use in a well-ventilated area is recommended.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Lauric acid is listed as a food additive in the EAFUS list compiled by the FDA. Reported in the EPA TSCA Inventory.

17 Related Substances

Capric acid; myristic acid; palmitic acid; sodium laurate; stearic acid.

Capric acid

Empirical formula: $C_{10}H_{20}O_2$
Molecular weight: 172.2
CAS number: [334-48-5]
Synonyms: *n*-capric acid; caprinic acid; caprynic acid; carboxylic acid C_{10}; decanoic acid; *n*-decanoic acid; decoic acid; decyclic acid; *n*-decylic acid; 1-nonanecarboxylic acid.
Appearance: white to pale yellow crystals with an unpleasant odor.
Acid value: 320–330
Boiling point: 270°C
Melting point: 31.5°C
Refractive index: $n_D^{40} = 1.4288$
Comments: capric acid is used as a flavoring agent in pharmaceutical preparations, providing a citrus-like flavor. It is used in cosmetics as an emulsifying agent. A specification for capric acid is included in the Food Chemicals Codex (FCC). The EINECS number for capric acid is 206-376-4.

Sodium laurate

Empirical formula: $C_{12}H_{23}O_2Na$
Molecular weight: 222.34
CAS number: [629-25-4]
Comments: sodium laurate is used as an emulsifying agent and surfactant in cosmetics. The EINECS number for sodium laurate is 211-082-4.

18 Comments

Although not included in any pharmacopeias, a specification for lauric acid is contained in the Food Chemicals Codex (FCC);(25) *see* Table I.

The EINECS number for lauric acid is 205-582-1.

19 Specific References

1 Kravchenko IA, Golovenko NY, Larionov VB, *et al.* Effect of lauric acid on transdermal penetration of phenazepam *in vivo*. *Bull Exp Biol Med* 2003; **136**(6): 579–581.
2 Chisty MNA, Bellantone RA, Taft DR, Plakogiannis FM. *In vitro* evaluation of the release of albuterol sulfate from polymer gels: effect of fatty acids on drug transport across biological membranes. *Drug Dev Ind Pharm* 2002; **28**(10): 1221–1229.
3 Stott PW, Williams AC, Barry BW. Mechanistic study into the enhanced transdermal permeation of a model beta-blocker, propranolol, by fatty acids: A melting point depression effect. *Int J Pharm* 2001; **219**(1–2): 161–176.
4 Morimoto K, Haruta T, Tojima H, Takeuchi Y. Enhancing mechanisms of saturated fatty acids on the permeations of indomethacin and 6-carboxyfluorescein through rat skins. *Drug Dev Ind Pharm* 1995; **21**(17): 1999–2012.
5 Ogiso T, Iwak IM, Hirota T, *et al.* Comparison of the *in vitro* penetration of propiverine with that of terodiline. *Biol Pharm Bull* 1995; **18**(7): 968–975.
6 Aungst BJ, Blake JA, Hussain MA. Contributions of drug solubilization, partitioning, barrier disruption, and solvent permeation to the enhancement of skin permeation of various compounds with fatty acids and amines. *Pharm Res* 1990; **7**(7): 712–718.
7 Ogiso T, Shintani M. Mechanism for the enhancement effect of fatty acids on the percutaneous absorption of propranolol. *J Pharm Sci* 1990; **79**(12): 1065–1071.
8 Pfister WR, Hsieh DST. Permeation enhancers compatible with transdermal drug delivery systems. Part I: Selection and formulation considerations. *Pharm Technol* 1990; **14**(9): 132–140.
9 Green PG, Hadgraft J, Wolff M. Physicochemical aspects of the transdermal delivery of bupranolol. *Int J Pharm* 1989; **55**(2–3): 265–269.
10 Green PG, Guy RH, Hadgraft J. *In vitro* and *in vivo* enhancement of skin permeation with oleic and lauric acids. *Int J Pharm* 1988; **48**(1–3): 103–111.
11 Green PG, Hadgraft J. Facilitated transfer of cationic drugs across a lipoidal membrane by oleic acid and lauric acid. *Int J Pharm* 1987; **37**(3): 251–255.
12 Ogiso T, Iwaki M, Kashitani Y, Yamashita K. Enhancement effect of lauric acid on the rectal absorption of propranolol from suppository in rats. *Chem Pharm Bull* 1991; **39**(10): 2657–2661.
13 Muranishi S. Characteristics of drug absorption via the rectal route. *Methods Find Exp Clin Pharmacol* 1984; **12**: 763–772.
14 Shojaei AH, Chang RK, Guo X, *et al.* Systemic drug delivery via the buccal mucosal route. *Pharm Technol* 2001; **25**(6): 70–81.
15 Constantinides PP, Welzel G, Ellens H, *et al.* Water-in-oil microemulsions containing medium-chain fatty acids/salts: formulation and intestinal absorption enhancement evaluation. *Pharm Res* 1996; **13**(2): 210–215.
16 Yamada K, Murakami M, Yamamoto A, *et al.* Improvement of intestinal absorption of thyrotropin-releasing hormone by chemical modification with lauric acid. *J Pharm Pharmacol* 1992; **44**(9): 717–721.
17 Buszello K, Harnisch S, Muller RH, Muller BW. The influence of alkali fatty acids on the properties and the stability of parenteral O/W emulsions modified with Solutol HS 15. *Eur J Pharm Biopharm* 2000; **49**(2): 143–149.
18 Gupta PK, Hickey AJ. Contemporary approaches in aerosolized drug delivery to the lung. *J Control Release* 1991; **17**(2): 129–147.
19 Health Evaluation Report on Lauric Acid Exposure during Flaking and Bagging Operations at Emery Industries, Los Angeles, CA. *National Institute for Occupational Safety and Health, HHE 80-160-897, NTIS Doc.* No. PB 82-25694-2, 1981.

Table I: FCC specification for lauric acid.(24)

Test	FCC 1996
Acid value	252–287
Heavy metals	⩽10 mg/kg
Iodine value	⩽3
Residue on ignition	⩽0.1%
Saponification value	253–287
Solidification point	26–44°C
Unsaponifiable matter	⩽0.3%
Water	⩽0.2%

20 Final report on the safety assessment of oleic acid, lauric acid, palmitic acid, myristic acid, and stearic acid. *J Am Coll Toxicol* 1987; **6**(3): 321–401.

21 Verschueren K, ed. *Handbook of Environmental Data of Organic Chemicals*, 2nd edn. New York: Van Nostrand Reinhold, 1983: 793.

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24 Oro R, Wretlind A. Pharmacological effects of fatty acids, triolein, and cottonseed oil. *Acta Pharmacol Toxicol* 1961; **18**: 141.

25 *Food Chemicals Codex*, 4th edn. Washington, DC: National Academy Press, 1996: 218.

20 General References

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21 Authors

PE Luner.

22 Date of Revision

19 August 2005.

Lecithin

1 Nonproprietary Names

USPNF: Lecithin
See also Section 4.

2 Synonyms

E322; egg lecithin; *LSC 5050*; *LSC 6040*; mixed soybean phosphatides; ovolecithin; *Phosal 53 MCT*; *Phospholipon 100 H*; soybean lecithin; soybean phospholipids; *Sternpur*; vegetable lecithin.

3 Chemical Name and CAS Registry Number

Lecithin [8002-43-5]

The chemical nomenclature and CAS Registry numbering of lecithin is complex. The commercially available lecithin, used in cosmetics, pharmaceuticals, and food products, is a complex mixture of phospholipids and other materials. However, it may be referred to in some literature sources as 1,2-diacyl-*sn*-glycero-3-phosphocholine (trivial chemical name, phosphatidylcholine). This material is the principal constituent of egg lecithin and has the same CAS Registry Number. The name lecithin and the CAS Registry Number above are thus used to refer to both lecithin and phosphatidylcholine in some literature sources.

Another principal source of lecithin is from an extract of soybeans (CAS [8030-76-0]). Egg yolk lecithin (CAS [93685-90-6]) is also listed in *Chemical Abstracts*.

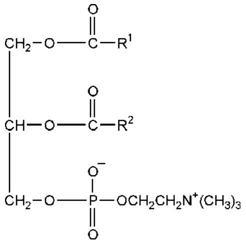
See also Section 4.

4 Empirical Formula and Molecular Weight

The USPNF 23 describes lecithin as a complex mixture of acetone-insoluble phosphatides that consists chiefly of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol, combined with various amounts of other substances such as triglycerides, fatty acids, and carbohydrates as separated from a crude vegetable oil source.

The composition of lecithin (and hence also its physical properties) varies enormously depending upon the source of the lecithin and the degree of purification. Egg lecithin, for example, contains 69% phosphatidylcholine and 24% phosphatidylethanolamine, while soybean lecithin contains 21% phosphatidylcholine, 22% phosphatidylethanolamine, and 19% phosphatidylinositol, along with other components.(1)

5 Structural Formula



α-Phosphatidylcholine

R^1 and R^2 are fatty acids, which may be different or identical.

Lecithin is a complex mixture of materials; *see* Section 4. The structure above shows phosphatidylcholine, the principal component of egg lecithin, in its α-form. In the β-form, the phosphorus-containing group and the R^2 group exchange positions.

6 Functional Category

Emollient; emulsifying agent; solubilizing agent.

7 Applications in Pharmaceutical Formulation or Technology

Lecithins are used in a wide variety of pharmaceutical applications; *see* Table I. They are also used in cosmetics(2) and food products.

Lecithins are mainly used in pharmaceutical products as dispersing, emulsifying, and stabilizing agents and are included in intramuscular and intravenous injections, parenteral nutrition formulations, and topical products such as creams and ointments.

Lecithins are also used in suppository bases,(3) to reduce the brittleness of suppositories, and have been investigated for their absorption-enhancing properties in an intranasal insulin formulation.(4) Lecithins are also commonly used as a component of enteral and parenteral nutrition formulations.

There is evidence that phosphatidylcholine (a major component of lecithin) is important as a nutritional supplement to fetal and infant development. Furthermore, choline is a required component of FDA-approved infant formulas.(5) Other studies have indicated that lecithin can protect against alcohol cirrhosis of the liver, lower serum cholesterol levels, and improve mental and physical performance.(6)

Liposomes in which lecithin is included as a component of the bilayer have been used to encapsulate drug substances; their potential as novel delivery systems has been investigated.(7) This application generally requires purified lecithins combined in specific proportions.

Therapeutically, lecithin and derivatives have been used as a pulmonary surfactant in the treatment of neonatal respiratory distress syndrome.

Table I: Uses of lecithin.

Use	Concentration (%)
Aerosol inhalation	0.1
IM injection	0.3–2.3
Oral suspensions	0.25–10.0

8 Description

Lecithins vary greatly in their physical form, from viscous semiliquids to powders, depending upon the free fatty acid content. They may also vary in color from brown to light yellow, depending upon whether they are bleached or unbleached or on the degree of purity. When they are exposed to air, rapid oxidation occurs, also resulting in a dark yellow or brown color.

Lecithins have practically no odor. Those derived from vegetable sources have a bland or nutlike taste, similar to that of soybean oil.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for lecithin.

Test	USPNF 23
Water	⩽1.5%
Lead	⩽0.001%
Heavy metals	⩽20 μg/g
Acid value	+
Hexane-insoluble matter	⩽0.3%
Acetone-insoluble matter	—
Organic volatile impurities	+

10 Typical Properties

Density:
0.97 g/cm^3 for liquid lecithin;
0.5 g/cm^3 for powdered lecithin.
Iodine number:
95–100 for liquid lecithin;
82–88 for powdered lecithin.
Isoelectric point: ≈3.5
Saponification value: 196
Solubility: lecithins are soluble in aliphatic and aromatic hydrocarbons, halogenated hydrocarbons, mineral oil, and fatty acids. They are practically insoluble in cold vegetable and animal oils, polar solvents, and water. When mixed with water, however, lecithins hydrate to form emulsions.

11 Stability and Storage Conditions

Lecithins decompose at extreme pH. They are also hygroscopic and subject to microbial degradation. When heated, lecithins oxidize, darken, and decompose. Temperatures of 160–180°C will cause degradation within 24 hours.

Fluid or waxy lecithin grades should be stored at room temperature or above; temperatures below 10°C may cause separation.

All lecithin grades should be stored in well-closed containers protected from light and oxidation. Purified solid lecithins should be stored in tightly closed containers at subfreezing temperatures.

12 Incompatibilities

Incompatible with esterases owing to hydrolysis.

13 Method of Manufacture

Lecithins are essential components of cell membranes and, in principle, may be obtained from a wide variety of living matter. In practice, however, lecithins are usually obtained from vegetable products such as soybean, peanut, cottonseed, sunflower, rapeseed, corn, or groundnut oils. Soybean lecithin is the most commercially important vegetable lecithin. Lecithin obtained from eggs is also commercially important and was the first lecithin to be discovered.

Vegetable lecithins are obtained as a by-product in the vegetable oil refining process. Polar lipids are extracted with hexane and, after removal of the solvent, a crude vegetable oil is obtained. Lecithin is then removed from the crude oil by water extraction. Following drying, the lecithin may be further purified.(1)

With egg lecithin, a different manufacturing process must be used since the lecithin in egg yolks is more tightly bound to proteins than in vegetable sources. Egg lecithin is thus obtained by solvent extraction from liquid egg yolks using acetone or from freeze-dried egg yolks using ethanol (95%).(1)

Synthetic lecithins may also be produced.

14 Safety

Lecithin is a component of cell membranes and is therefore consumed as a normal part of the diet. Although excessive consumption may be harmful, it is highly biocompatible and oral doses of up to 80 g daily have been used therapeutically in the treatment of tardive dyskinesia.(8) When used in topical formulations, lecithin is generally regarded as a nonirritant and nonsensitizing material.(2) The Cosmetic Ingredients Review Expert Panel (CIR) has reviewed lecithin and issued a tentative report revising the safe concentration of the material from 1.95% to 15.0% in rinse-off and leave-in products. They note, however, that there are insufficient data to rule on products that are likely to be inhaled.(9)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Lecithins may be irritant to the eyes; eye protection and gloves are recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (inhalations; IM and IV injections; otic preparations; oral capsules, suspensions and tablets; rectal, topical, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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18 Comments

Poloxamer lecithin organogels have been used in topical formulations for the delivery of non-steroidal anti-inflammatory drugs.(10)

Lecithins contain a variety of unspecified materials; care should therefore be exercised in the use of unpurified lecithin in injectable or topical dosage forms, as interactions with the active substance or other excipients may occur. Unpurified lecithins may also have a greater potential for irritancy in formulations.

Supplier's literature should be consulted for information on the different grades of lecithin available and their applications in formulations.

A specification for lecithin is contained in the Food Chemicals Codex (FCC). The EINECS number for lecithin is 232-307-2.

19 Specific References

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20 General References

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Hanin I, Pepeu G, eds. *Phospholipids: Biochemical, Pharmaceutical and Analytical Considerations*. New York: Plenum Press, 1990.

21 Authors

K Fowler.

22 Date of Revision

24 August 2005.

Leucine

1 Nonproprietary Names

JP: L-Leucine
PhEur: Leucinum
USP: Leucine

2 Synonyms

α-Aminoisocaproic acid; L-α-aminoisocaproic acid; 2-amino-4-methylpentanoic acid; 2-amino-4-methylvaleric acid; α-amino-γ-methylvaleric acid; 1,2-amino-4-methylvaleric acid; DL-leucine; L-leucine; leu; 4-methylnorvaline.

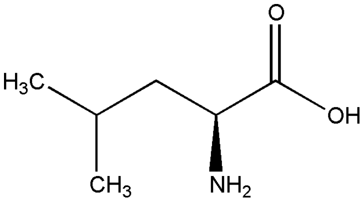
3 Chemical Name and CAS Registry Number

L-Leucine [61-90-5]

4 Empirical Formula and Molecular Weight

$C_6H_{13}NO_2$ 131.20

5 Structural Formula



6 Functional Category

Antiadherent; flavoring agent; lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Leucine is used in pharmaceutical formulations as a flavoring agent.(1) It has been used experimentally as an antiadherent to improve the deagglomeration of disodium cromoglycate microparticles in inhalation preparations;(2) and as a tablet lubricant.(3) Leucine copolymers have been shown to successfully produce stable drug nanocrystals in water.(4)

8 Description

Leucine occurs as a white or almost off-white crystalline powder or shiny flakes.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for leucine.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	+	+	—
Optical rotation	+14.5° to +16.0°	+14.5° to +16.0°	+14.9° to +17.3°
pH	5.5–6.5	—	5.5–7.0
Appearance of solution	+	+	—
Chloride	⩽0.021%	⩽200 ppm	⩽0.05%
Sulfate	⩽0.028%	⩽300 ppm	⩽0.03%
Ammonium	⩽0.02%	⩽200 ppm	—
Ninhydrin-positive substances	—	+	—
Iron	—	⩽10 ppm	⩽0.003%
Heavy metals	⩽20 ppm	⩽10 ppm	⩽0.0015%
Arsenic	⩽2 ppm	—	—
Other amino acids	+	—	—
Loss on drying	⩽0.30%	⩽0.5%	⩽0.2%
Residue on ignition	⩽0.10%	⩽0.1%	⩽0.4%
Organic volatile impurities	—	—	+
Assay	⩾98.5%	98.5–101.5%	98.5–101.5%

10 Typical Properties

Density: 1.293 g/cm^3
Dissociation constant: $pK_a = 2.35$ at 13°C.
Isoelectric point: 6.04
Melting point: 293°C
Solubility: soluble in acetic acid, ethanol (99%) and water. Practically insoluble in ether.

11 Stability and Storage Conditions

Leucine is sensitive to light and moisture and should be stored in an airtight container in a cool, dark, dry place.

12 Incompatibilities

Leucine is incompatible with strong oxidizing agents.

13 Method of Manufacture

Leucine is produced microbially by incubating an amino-acid-producing microorganism including but not exclusive to *Pseudomonas*, *Escherichia*, *Bacillus*, or *Staphylococcus* in the presence of oxygen and a hydrocarbon. The nutrient medium should contain an inhibitory amount of a growth inhibitor that is a chemically similar derivative of leucine, e.g: methylallylglycine, α-hydrozinoisocaproic acid, or β-cyclopentanealanine, so as to inhibit the growth of the organism except for at least one mutant that is resistant to the inhibitory effect. The resistant mutant is then isolated and grown in the presence of oxygen and the hydrocarbon in the absence of the inhibitor. The mutant cells are then harvested and a nutrient medium is formed that includes a hydrocarbon as the sole source of carbon. Finally, the harvested cells are incubated in the medium in the presence of oxygen.(5)

14 Safety

Leucine is an essential amino acid and is consumed as part of a normal diet. It is generally regarded as a nontoxic and nonirritant material. It is moderately toxic by the subcutaneous route.

LD_{50} (rat, IP): 5.379 g/kg(6)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IV infusion; oral tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

DL-Leucine

DL-Leucine
Empirical formula: $C_6H_{13}NO_2$
Molecular weight: 131.20
Appearance: white leaflets.
Dissociation constant:
$pK_{a1} = 2.36$;
$pK_{a2} = 9.60$.
Solubility: soluble in ethanol (90%) and water. Practically insoluble in ether.

18 Comments

A specification for leucine is included in the Food Chemicals Codex (FCC). The EINECS number for leucine is 200-522-0.

19 Specific References

1 Ash M, Ash I. *Handbook of Pharmaceutical Additives*, 2nd edn. Endicott, NY: Synapse Information Resources, 2002: 542.
2 Abdolhossien RN, Kambiz G, Mohahhadali B, Morteza R. The effect of vehicle on physical properties and aerosolisation behaviour of disodium cromoglycate microparticles spray dried alone or with L-leucine. *Int J Pharm* 2004; **285**: 97–108.
3 Gusman S, Gregoriades D. Effervescent potassium chloride tablet. United States Patent No. 3,903,255; 1975.
4 Lee J, Lee SJ, Choi JY, *et al*. Amphiphilic amino acid copolymers as stabilizers for the preparation of nanocrystal dispersion. *Eur J Pharm Sci* 2005; **24**: 441–449.
5 Mobil Oil Corp. Synthesis of amino acids. UK Patent No. 1 071 935; 1967.
6 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 2224.

20 General References

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21 Authors

GE Amidon.

22 Date of Revision

25 August 2005.

Linoleic Acid

1 Nonproprietary Names

None adopted.

2 Synonyms

Emersol 310; *Emersol 315*; leinoleic acid; 9-*cis*,12-*cis*-linoleic acid; 9,12-linoleic acid; linolic acid; *cis*,*cis*-9,12-octadecadienoic acid; *Pamolyn*; *Polylin No. 515*; telfairic acid.

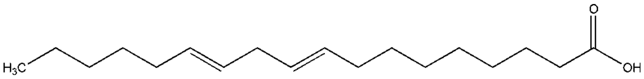
3 Chemical Name and CAS Registry Number

(*Z*,*Z*)-9,12-Octadecadienoic acid [60-33-3]

4 Empirical Formula and Molecular Weight

$C_{18}H_{32}O_2$ 280.45

5 Structural Formula



6 Functional Category

Dietary supplement; emulsifying agent; skin penetrant.

7 Applications in Pharmaceutical Formulation or Technology

Linoleic acid is used in topical transdermal formulations,(1–14) in oral formulations as an absorption enhancer,(15,16) and in topical cosmetic formulations as an emulsifying agent.(17) It is also administered in parenteral emulsions as a dietary supplement.

8 Description

Linoleic acid occurs as a colorless to light-yellow-colored oil.

9 Pharmacopeial Specifications

See Section 18.

10 Typical Properties

Boiling point: 230°C at 16 mmHg
Density: 0.9007 g/cm^3
Iodine value: 181.1
Melting point: –5°C
Refractive index: n_D^{20} = 1.4699
Solubility: freely soluble in ether; soluble in ethanol (95%); miscible with dimethylformamide, fat solvents, and oils.

11 Stability and Storage Conditions

Linoleic acid is sensitive to air, light, moisture, and heat. It should be stored in a tightly sealed container under an inert atmosphere and refrigerated.

12 Incompatibilities

Linoleic acid is incompatible with bases, strong oxidizing agents, and reducing agents.

13 Method of Manufacture

Linoleic acid is obtained by extraction from various vegetable oils such as safflower oil.

14 Safety

Linoleic acid is widely used in cosmetics and topical pharmaceutical formulations and is generally regarded as a nontoxic material. On exposure to the eyes, skin, and mucous membranes, linoleic acid can cause mild irritation.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Gloves and eye protection are recommended.

16 Regulatory Status

GRAS listed. Approved for use in foods in Europe and the USA.

17 Related Substances

Ethyl linoleate; methyl linoleate.

Ethyl linoleate

Empirical formula: $C_{20}H_{36}O_2$
CAS number: [544-35-4]
Synonyms: linoleic acid ethyl ester; 9,12-octadecadienoic acid ethyl ester; vitamin F.
Comments: ethyl linoleate is used in pharmaceutical formulations as an emollient and humactent. It is also used as a solvent for fats. The EINECS number for ethyl linoleate is 208-868-4.

Methyl linoleate

Empirical formula: $C_{19}H_{34}O_2$
CAS number: [112-63-0]
Synonyms: 9,12-octadecadienoic acid, methyl ester.
Comments: methyl linoleate is used in cosmetics as an emollient. The EINECS number for methyl linoleate is 203-993-0.

18 Comments

Studies have shown that conjugated linoleic acid increases paracellular permeability across human intestinal-like Caco-2 cell monolayers, and consequently may also, as a dietary supplement, increase calcium absorption *in vivo*.(16)

Linoleic acid has been shown to reduce skin irritation following acute perturbations, exhibiting clinical effects that are comparable to glucocorticoids.(17)

A pre-emulsified linoleic acid system has been used to investigate the protective actions of phenolic compounds against lipid peroxidation.(18)

Although not included in any pharmacopeias, a specification for linoleic acid is contained in the Food Chemicals Codex (FCC); *see* Table I.

The EINECS number for linoleic acid is 200-470-9.

Table I: FCC Specification for linoleic acid.(19)

Test	FCC 1996
Identification	+
Acid value	196–202
Heavy metals	⩽10 mg/kg
Iodine value	145–160
Residue on ignition	⩽0.01%
Saponification value	194–202
Unsaponifiable matter	⩽2.0%
Water	⩽0.5%
Assay	⩾60%

19 Specific References

1 Gwak HS, Chun IK. Effect of vehicles and penetration enhancers on the *in vitro* percutaneous absorption of tenoxicam through hairless mouse skin. *Int J Pharm* 2002; **236**(1–2): 57–64.

2 Bhattachrya A, Ghosal SK. Effect of hydrophobic permeation enhancers on the release and skin permeation kinetics from matrix type transdermal drug delivery system of ketotifen fumarate. *Acta Pol Pharm* 2001; **58**(2): 101–105.

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5 Meaney CM, O'Driscoll CM. Comparison of the permeation enhancement potential of simple bile salt and mixed bile salt: fatty acid micellar systems using the Caco-2 cell culture model. *Int J Pharm* 2000; **207**(10): 21–30.

6 Effect of hydrophobic permeation enhancers on the release and skin permeation kinetics from matrix type transdermal drug delivery system of ketotifen fumarate. *Eastern Pharmacist* 2000; **43**: 109–112.

7 Tanojo H, Junginger HE. Skin permeation enhancement by fatty acids. *J Dispers Sci Technol* 1999; **20**(1–2): 127–138.

8 Bhatia KS, Singh J. Synergistic effect of iontophoresis and a series of fatty acids on LHRH permeability through porcine skin. *J Pharm Sci* 1998; **87**: 462–469.

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10 Carelli V, Di Colo G, Nannipieri E, Serafini MF. Enhancement effects in the permeation of alprazolam through hairless mouse skin. *Int J Pharm* 1992; **88**(8): 89–97.

11 Ibrahim SA, Hafez E, El-Shanawany SM, *et al.* Formulation and evaluation of some topical antimycotics. Part 3. Effect of promotors on the *in vitro* and *in vivo* efficacy of clotrimazole ointment. *Bull Pharm Sci Assiut Univ* 1991; **14**(1–2): 82–94.

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18 Cheng Z, Ren J, Li Y, *et al.* Establishment of a quantitative structure–activity relationship model for evaluating and predicting the protective potentials of phenolic antioxidants on lipid peroxidation. *J Pharm Sci* 2003; **92**(3): 475–484.

19 *Food Chemicals Codex*, 4th edn. Washington, DC: National Academy Press, 1996: 227.

20 General References

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21 Authors

MS Tesconi.

22 Date of Revision

9 August 2005.

Macrogol 15 Hydroxystearate

1 Nonproprietary Names

BP: Macrogol 15 hydroxystearate
PhEur: Macrogoli 15 hydroxystearas

2 Synonyms

12-Hydroxyoctadecanoic acid polymer with α-hydro-ω-hydroxypoly(oxy-1,2-ethanediyl); polyethylene glycol 660 12-hydroxystearate; *Solutol HS 15*.

3 Chemical Name and CAS Registry Number

Polyethylene glycol-15-hydroxystearate [70142-34-6]

4 Empirical Formula and Molecular Weight

The PhEur 2005 describes macrogol 15 hydroxystearate as a mixture of mainly monoesters and diesters of 12-hydroxystearic acid and macrogols obtained by the ethoxylation of 12-hydroxystearic acid. The number of moles of ethylene oxide reacted per mole of 12-hydroxystearic acid is 15 (nominal value). It contains about 30% free macrogols.

5 Structural Formula

See Section 4.

6 Functional Category

Dissolution enhancer; nonionic surfactant; solubilizing agent.

7 Applications in Pharmaceutical Formulation or Technology

Macrogol 15 hydroxystearate is frequently used in preclinical testing of drugs, mainly for IV and other parenteral applications.(1–4) The solubilizing capacity for some tested drugs (clotrimazole, carbamazepine, 17β-estradiol, sulfathiazole, and piroxicam) increases almost linearly with increasing concentration of solubilizing agent; *see* Figure 1. This is due to the formation of spherical micelles even at high concentrations of macrogol 15 hydroxystearate. Similarly, tests have revealed that viscosity increases with increasing amount of solubilizer, but the amount of solubilized drugs does not have any additional influence on the kinematic viscosity; *see* Figure 2. Lipid nanocapsules comprising macrogol 15 hydroxystearate and soybean phosphatidylcholine containing 3% docetaxel have been successfully prepared by a solvent-free inversion process.

8 Description

Macrogol 15 hydroxystearate is a yellowish-white waxy mass at room temperature, which becomes liquid at approximately 30°C.

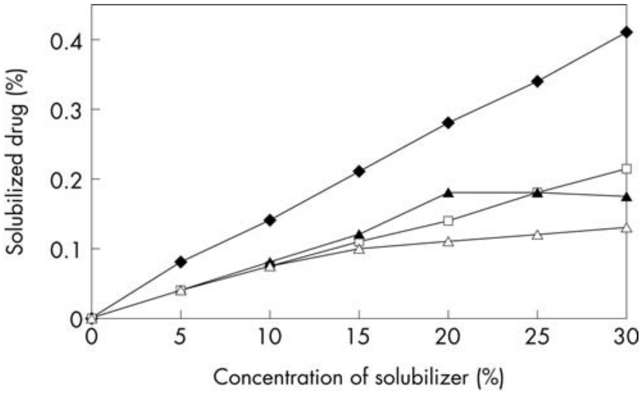

Figure 1: Solubilizing capacity of macrogol 15 hydroxystearate (*Solutol HS 15*, BASF Plc).
◆: *Solutol HS 15* with clotrimazole
□: *Solutol HS 15* with 17β-estradiol
▲: Polysorbate 80 with clotrimazole
△: Polysorbate 80 with 17β-estradiol

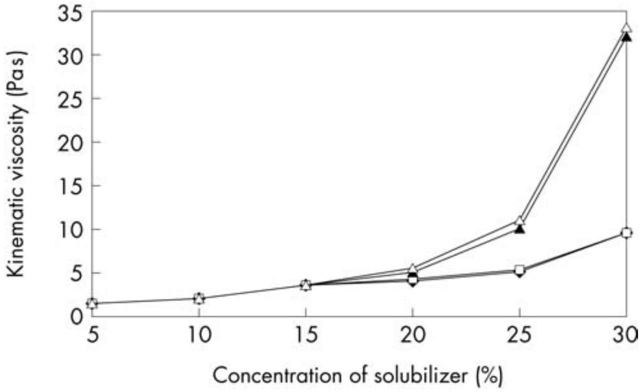

Figure 2: Kinematic viscosity of macrogol 15 hydroxystearate (*Solutol HS 15*, BASF Plc).
◆: *Solutol HS 15*
□: *Solutol HS 15* with clotrimazole
▲: Polysorbate 80
△: Polysorbate 80 with clotrimazole

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acidity/alkalinity: pH = 6–7 (10% w/v aqueous solution at 20°C)
Critical micelle concentration: 0.005–0.02%
Density: 1.03 g/cm^3
Flash point: 272°C
HLB value: 14–16
Ignition temperature: 360°C

Table I: Pharmacopeial specifications for macrogol 15 hydroxystearate.

Test	PhEur 2005
Identification	+
Characters	+
Solution appearance	+
Acid value	⩽1.0
Hydroxyl value	90–110
Iodine value	⩽2.0
Peroxide value	⩽5.0
Saponification value	53–63
Free macrogols	27.0–39.0%
Ethylene oxide	⩽1 ppm
Dioxane	⩽50 ppm
Nickel	⩽1 ppm
Water	⩽1%
Total ash	⩽0.3%

Solidification temperature: 25–30°C

Solubility: soluble in ethanol, propan-2-ol, and water to form clear solutions. The solubility in water decreases with increasing temperature. It is insoluble in liquid paraffin.

Viscosity (dynamic): 12 mPa s (12 cP) for a 30% w/v aqueous solution at 25°C; 73 mPa s (73 cP) for a 30% w/v aqueous solution at 60°C.

11 Stability and Storage Conditions

Macrogol 15 hydroxystearate has a high chemical stability. The prolonged action of heat may induce physical separation into a liquid and a solid phase after cooling, which can be reversed by subsequent homogenization. Macrogol 15 hydroxystearate is stable for at least 24 months if stored in unopened airtight containers at room temperature (maximum 25°C). Aqueous solutions of macrogol 15 hydroxystearate can be heat-sterilized (121°C, 2.1 bar). The pH may drop slightly during heating, which should be taken into account. Separation into phases may also occur, but agitating the hot solution can reverse this. Aqueous solutions can be stabilized with the standard preservatives used in pharmaceuticals.

12 Incompatibilities

—

13 Method of Manufacture

Macrogol 15 hydroxystearate is produced by reacting 15 moles of ethylene oxide with 1 mole of 12-hydroxystearic acid.

14 Safety

Macrogol 15 hydroxystearate is used in parenteral pharmaceutical preparations in concentrations up to 50% to solubilize diclofenac, propanidid, and vitamin K1. It has also been used in preclinical formulations in preparing supersaturated injectable formulations of water-insoluble molecules. It is generally regarded as a relatively nontoxic and nonirritant excipient.

Macrogol 15 hydroxystearate is reported to not be mutagenic in bacteria, mammalian cell cultures and mammals.

LD_{50} (rat, oral): >20 g/kg(5)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

—

17 Related Substances

Polyethylene glycol.

18 Comments

Macrogol 15 hydroxystearate is not restricted solely to parenteral use, but is also suitable for oral applications.

19 Specific References

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20 General References

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Smith DB, Ewen C, Mackintosh J, *et al.* A phase I and pharmacokinetic study of amphethinile. *Br J Cancer* 1988; **57**: 623–627.

Woodburn K, Sykes E, Kessel D. Interactions of Solutol HS 15 and Cremophor EL with plasma lipoproteins. *Int J Biochem Cell Biol* 1995; **27**: 693–699.

21 Authors

J-P Mittwollen, T Schmeller.

22 Date of Revision

25 May 2005.

Magnesium Aluminum Silicate

1 Nonproprietary Names

BP: Aluminium magnesium silicate
PhEur: Aluminii magnesii silicas
USPNF: Magnesium aluminum silicate

2 Synonyms

Aluminosilicic acid, magnesium salt; aluminum magnesium silicate; *Carrisorb*; *Gelsorb*; *Magnabite*; magnesium aluminosilicate; magnesium aluminum silicate, colloidal; magnesium aluminum silicate, complex colloidal; *Neusilin*; *Pharmsorb*; silicic acid, aluminum magnesium salt; *Veegum*.

3 Chemical Name and CAS Registry Number

Aluminum magnesium silicate	[12511-31-8]
Magnesium aluminum silicate	[1327-43-1]

4 Empirical Formula and Molecular Weight

Magnesium aluminum silicate is a polymeric complex of magnesium, aluminum, silicon, oxygen, and water. The average chemical analysis is conventionally expressed as oxides:

Silicon dioxide	61.1%
Magnesium oxide	13.7%
Aluminum oxide	9.3%
Titanium dioxide	0.1%
Ferric oxide	0.9%
Calcium oxide	2.7%
Sodium oxide	2.9%
Potassium oxide	0.3%
Carbon dioxide	1.8%
Water of combination	7.2%

5 Structural Formula

The complex is composed of a three-lattice layer of octahedral alumina and two tetrahedral silica sheets. The aluminum is substituted to varying degrees by magnesium (with sodium or potassium for balance of electrical charge). Additional elements present in small amounts include iron, lithium, titanium, calcium, and carbon.

6 Functional Category

Adsorbent; stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Magnesium aluminum silicate has been used for many years in the formulation of tablets, ointments, and creams. It is used in oral and topical formulations as a suspending and stabilizing agent either alone or in combination with other suspending agents.(1–3) The viscosity of aqueous dispersions may be greatly increased by combination with other suspending agents, such as xanthan gum, owing to synergistic effects, *see* Xanthan Gum. In tablets, magnesium aluminum silicate is used as a binder and disintegrant in conventional or slow-release formulations.(4,5) *See* Table I.

Magnesium aluminum silicate may cause bioavailability problems with certain drugs, *see* Section 12.

Table I: Uses of magnesium aluminum silicate.

Use	Concentration (%)
Adsorbent	10–50
Binding agent	2–10
Disintegrating agent	2–10
Emulsion stabilizer (oral)	1–5
Emulsion stabilizer (topical)	2–5
Suspending agent (oral)	0.5–2.5
Suspending agent (topical)	1–10
Stabilizing agent	0.5–2.5
Viscosity modifier	2–10

8 Description

The USPNF 23 describes magnesium aluminum silicate as a blend of colloidal montmorillonite and saponite that has been processed to remove grit and nonswellable ore components. Four types of magnesium aluminum silicate are defined: types IA, IB, IC, and IIA. These types differ according to their viscosity and ratio of aluminum and magnesium content, *see* Table II.

The PhEur 2005 describes magnesium aluminum silicate (aluminium magnesium silicate) as a mixture of particles with colloidal particle size of montmorillonite and saponite, free from grit and nonswellable ore.

Magnesium aluminum silicate occurs as off-white to creamy white, odorless, tasteless, soft, slippery small flakes, or as a fine, micronized powder. Flakes vary in shape and size from about 0.3×0.4 mm to 1.0×2.0 mm and about 25–240 μm thick. Many flakes are perforated by scattered circular holes 20–120 μm in diameter. Under dark-field polarized light, innumerable bright specks are observed scattered over the flakes. The powder varies from 45 to 297 μm in size.

Table II: Magnesium aluminum silicate types defined in the USPNF 23.

Type	Viscosity (mPa s)	Al content/ Mg content
IA	225–600	0.5–1.2
IB	150–450	0.5–1.2
IC	800–2200	0.5–1.2
IIA	100–300	1.4–2.8

9 Pharmacopeial Specifications

See Table III.

Table III: Pharmacopeial specifications for magnesium aluminum silicate.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Viscosity (5% w/v suspension)	—	*See* Table II
Microbial limits	$\leqslant 10^3$/g	$\leqslant 10^3$/g
pH (5% w/v suspension)	9.0–10.0	9.0–10.0
Acid demand	—	+
Loss on drying	$\leqslant$8.0%	$\leqslant$8.0%
Arsenic	$\leqslant$3 ppm	$\leqslant$3 ppm
Lead	$\leqslant$15 ppm	$\leqslant$0.0015%
Assay for Al and Mg content	95.0–105.0	+

10 Typical Properties

Acid demand: 6–8 mL of 0.1 N HCl is required to reduce the pH of 1 g to pH 4.

Density: 2.418 g/cm^3

Moisture content: 6.0–9.98%.(6) *See also* Figures 1, 2 and 3.(6)

Particle size distribution: *see* Section 8.

Solubility: practically insoluble in alcohols, water, and organic solvents.

Swelling capacity: swelling properties are reversible. Magnesium aluminum silicate swells to many times its original volume in water to form colloidal dispersions and may be dried and rehydrated any number of times.

Viscosity (dynamic): dispersions in water at the 1–2% w/v level are thin colloidal suspensions. At 3% w/v and above, dispersions are opaque. As the concentration is increased above 3% w/v, the viscosity of aqueous dispersions increases rapidly; at 4–5% w/v, dispersions are thick, white colloidal sols, while at 10% w/v firm gels are formed. Dispersions are thixotropic at concentrations greater than 3% w/v. The viscosity of the suspension increases with heating or addition of electrolytes, and at higher concentrations with aging.

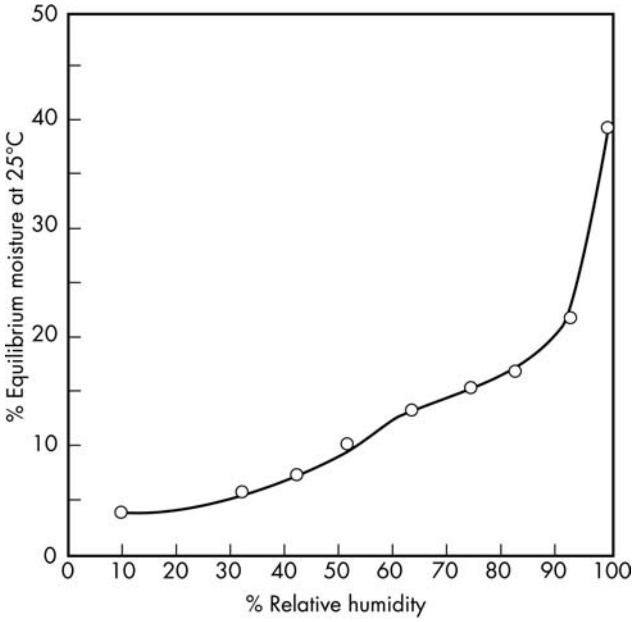


Figure 1: Equilibrium moisture content of magnesium aluminum silicate (*Veegum HV*).

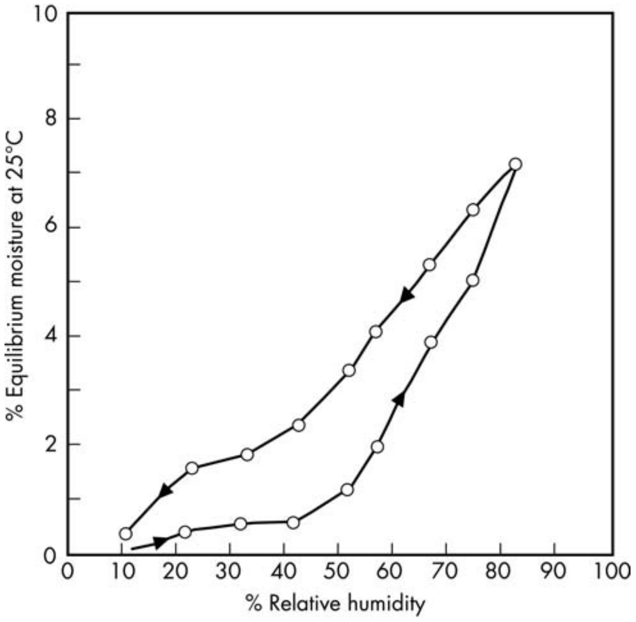


Figure 2: Sorption–desorption isotherm of magnesium aluminum silicate (*Pharmasorb*).

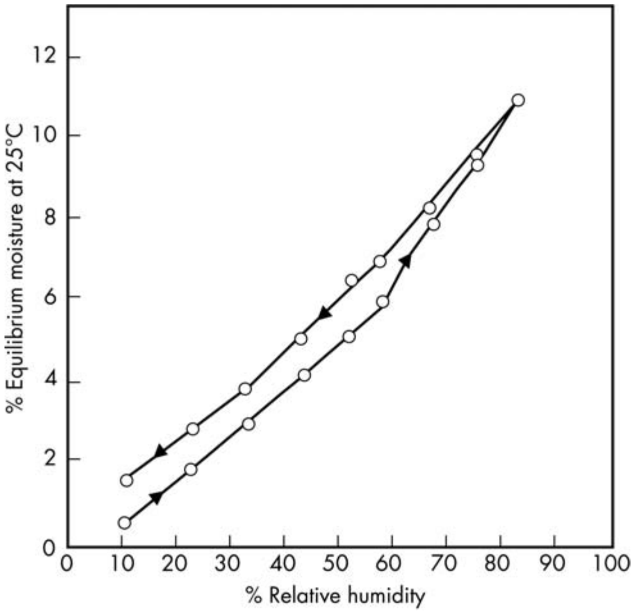


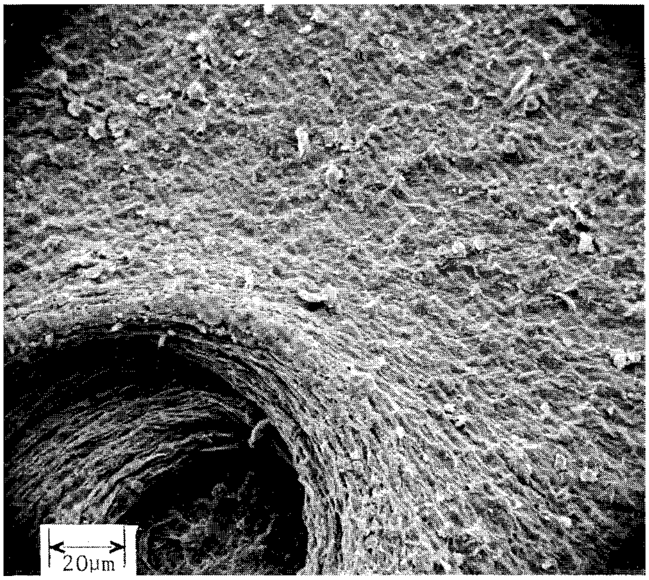
Figure 3: Sorption–desorption isotherm of magnesium aluminum silicate (*Pharmasorb colloidal*).

11 Stability and Storage Conditions

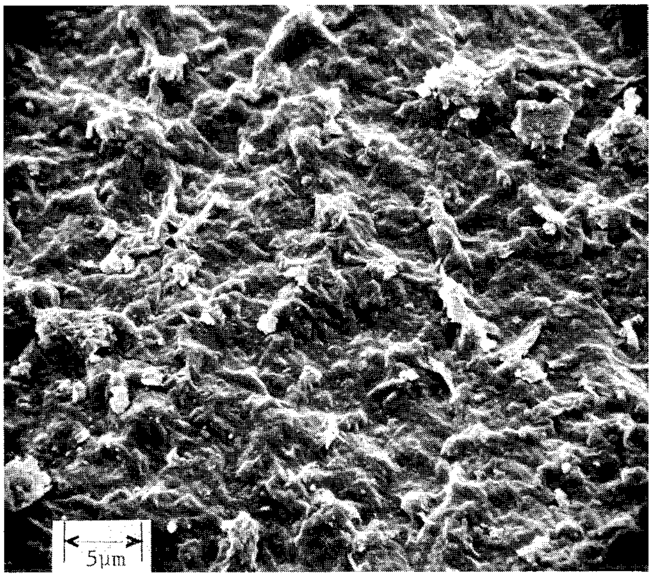
Magnesium aluminum silicate is stable indefinitely when stored under dry conditions. It is stable over a wide pH range, has base-exchange capacity, absorbs some organic substances, and is compatible with organic solvents.

Magnesium aluminum silicate should be stored in a well-closed container, in a cool, dry place.

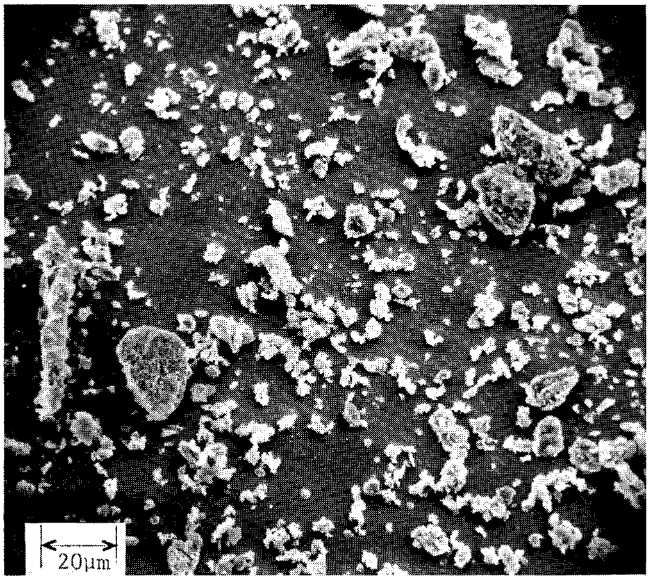
SEM: 1
Excipient: magnesium aluminum silicate (*Veegum*)
Manufacturer: RT Vanderbilt Co., Inc.
Lot No.: 61A-1
Magnification: 600×
Voltage: 10 kV



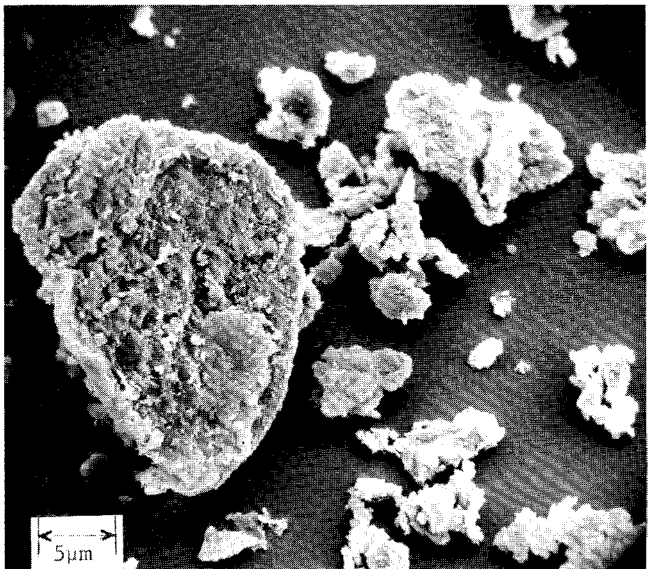
SEM: 2
Excipient: magnesium aluminum silicate (*Veegum*)
Manufacturer: RT Vanderbilt Co., Inc.
Lot No.: 61A-1
Magnification: 2400×
Voltage: 10 kV



SEM: 3
Excipient: magnesium aluminum silicate (*Veegum F*)
Manufacturer: RT Vanderbilt Co., Inc.
Lot No: 61A-2
Magnification: 600×
Voltage: 10 kV



SEM: 4
Excipient: magnesium aluminum silicate (*Veegum F*)
Manufacturer: RT Vanderbilt Co., Inc.
Lot No.: 61A-2
Magnification: 2400×
Voltage: 10 kV



12 Incompatibilities

Owing to its inert nature, magnesium aluminum silicate has few incompatibilities but is generally unsuitable for acidic solutions below pH 3.5. Magnesium aluminum silicate, as with other clays, may adsorb some drugs.(7,8) This can result in low bioavailability if the drug is tightly bound or slowly desorbed, e.g., amfetamine sulfate,(4) tolbutamide,(9) warfarin sodium,(10) and diazepam.(11)

13 Method of Manufacture

Magnesium aluminum silicate is obtained from silicate ores of the montmorillonite group, which show high magnesium content. The ore is blended with water to form a slurry to remove impurities and separate out the colloidal fraction. The refined colloidal dispersion is drum-dried to form a small flake, which is then micro-atomized to form various powder grades.

14 Safety

Magnesium aluminum silicate is generally regarded as nontoxic and nonirritating at the levels employed as a pharmaceutical excipient. Subacute animal feeding studies in rats and dogs fed magnesium aluminum silicate at 10% of the diet, for 90 days, were negative, including autopsy and histopathological examinations.(12)

LD_{50} (rat, oral): > 16 g/kg(13)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Adequate ventilation should be provided and dust generation minimized.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral granules, solutions, suspensions and tablets; rectal; and topical preparations; vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Attapulgite; bentonite; kaolin; magnesium silicate; magnesium trisilicate; montmorillonite; saponite; talc.

Montmorillonite

Empirical formula: $Al_2O_5 \cdot 4SiO_2 \cdot 4H_2O$
CAS number: [1318-93-0]
Comments: a naturally occurring silicate clay.

18 Comments

The EINECS number for magnesium aluminum silicate is 215-478-8.

19 Specific References

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Yokoi H, Enomoto S, Takahashi H. Effect of magnesium aluminosilicate on fluidity of pharmaceutical powders [in Japanese]. *J Pharm Soc Jpn* 1978; **98**: 418–425.

21 Authors

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22 Date of Revision

8 August 2005.

Magnesium Carbonate

1 Nonproprietary Names

BP:	Heavy magnesium carbonate Light magnesium carbonate
JP:	Magnesium carbonate
PhEur:	Magnesii subcarbonas ponderosus Magnesii subcarbonas levis
USP:	Magnesium carbonate

2 Synonyms

Carbonic acid, magnesium salt (1:1); carbonate magnesium; hydromagnesite; E504. *See* Sections 4 and 17.

3 Chemical Name and CAS Registry Number

Magnesium carbonate anhydrous [546-93-0]
See also Sections 4 and 17.

4 Empirical Formula and Molecular Weight

Magnesium carbonate is not a homogeneous material but may consist of the normal hydrate, the basic hydrate, and the anhydrous material $MgCO_3$, which is rarely encountered. Basic magnesium carbonate is probably the most common form, and may vary in formula between light magnesium carbonate, $(MgCO_3)_3{\cdot}Mg(OH)_2{\cdot}3H_2O$, and magnesium carbonate hydroxide, $(MgCO_3)_4{\cdot}Mg(OH)_2{\cdot}5H_2O$. Normal magnesium carbonate is a hydrous magnesium carbonate with a varying amount of water, $MgCO_3{\cdot}xH_2O$.

See also Sections 8, 13 and 17.

5 Structural Formula

See Section 4.

6 Functional Category

Adsorbent; antacid; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

As an excipient, magnesium carbonate is mainly used as a directly compressible tablet diluent in concentrations up to 45% w/w. Heavy magnesium carbonate produces tablets with high crushing strength, low friability, and good disintegration properties.(1–4) However, magnesium carbonate can have varying effects on dissolution and stability.(5,6) *See also* Section 12. Magnesium carbonate has been incorporated in microsphere formulations for the purpose of stabilizing encapsulated proteins.(7) Magnesium carbonate is also used to absorb liquids, such as flavors, in tableting processes.

Magnesium carbonate is additionally used as a food additive and therapeutically as an antacid.

See Table I.

Table I: Uses of magnesium carbonate.

Use	Concentration (%)
Absorbent of liquid, in tableting	0.5–1.0
Tablet excipient (direct compression)	≤45

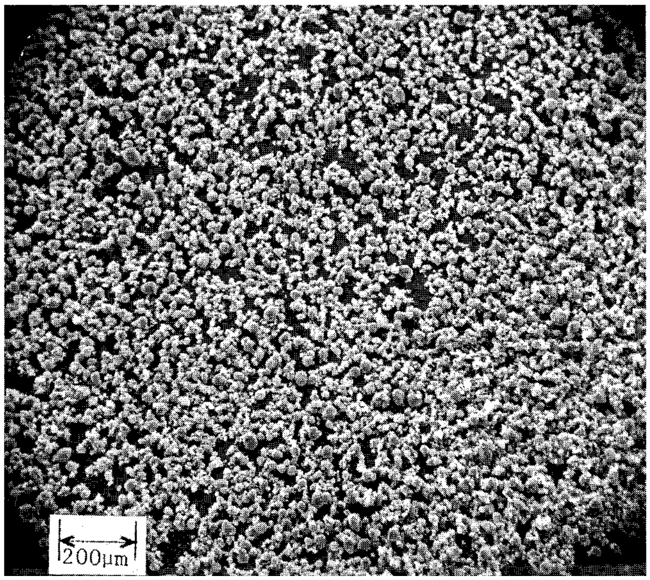
8 Description

Magnesium carbonate occurs as light, white-colored friable masses or as a bulky, white-colored powder. It has a slightly earthy taste and is odorless but, since it has a high absorptive ability, magnesium carbonate can absorb odors.

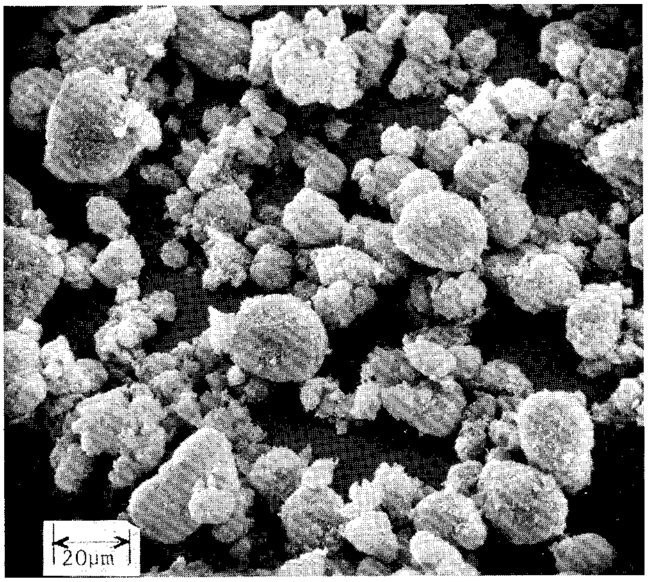
The USP 28 describes magnesium carbonate as either a basic hydrated magnesium carbonate or a normal hydrated magnesium carbonate. However, the PhEur 2005 describes magnesium carbonate as being a hydrated basic magnesium carbonate in two separate monographs: heavy magnesium carbonate and light magnesium carbonate. The molecular formulas for heavy magnesium carbonate and light magnesium carbonate vary, but heavy magnesium carbonate may generally be regarded as the tetrahydrate $[(MgCO_3)_3{\cdot}Mg(OH)_2{\cdot}4H_2O]$, while light magnesium carbonate may be regarded as the trihydrate $[(MgCO_3)_3{\cdot}Mg(OH)_2{\cdot}3H_2O]$.

The molecular weights of the heavy and light forms of magnesium carbonate are 383.32 and 365.30, respectively.

SEM: 1
Excipient: Magnesium carbonate USP
Manufacturer: Mallinckrodt Chemicals Co.
Lot No.: KJGJ
Magnification: 60×
Voltage: 20 kV



SEM: 2
Excipient: Magnesium carbonate USP
Manufacturer: Mallinckrodt Chemicals Co.
Lot No.: KJGJ
Magnification: 600×
Voltage: 20 kV



9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for magnesium carbonate.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	—	+	—
Microbial limits	—	—	+
Color of solution	—	+	—
Soluble salts	⩽10.0 mg	⩽1.0%	⩽1.0%
Acid-insoluble substances	⩽2.5 mg	⩽0.05%	⩽0.05%
Arsenic	⩽5 ppm	⩽2 ppm	⩽4 ppm
Calcium	⩽0.6%	⩽0.75%	⩽0.45%
Heavy metals	⩽30 ppm	⩽20 ppm	⩽0.003%
Iron	⩽200 ppm	⩽400 ppm	⩽0.02%
Chloride	—	⩽0.07%	—
Assay (as MgO)	40.0–44.0%	40.0–45.0%	40.0–43.5%

Note that except where indicated all of the PhEur 2005 test limits apply to both the heavy and light forms of magnesium carbonate.

10 Typical Properties

Angle of repose:
42–50° for granular heavy magnesium carbonate;
56–60° for spray-dried heavy magnesium carbonate.(3)

Density (bulk):
Heavy magnesium carbonate: 0.207–0.56 g/cm^3;(8)
Light magnesium carbonate: ≈0.12 g/cm^3.

Density (tapped):
Heavy magnesium carbonate: 0.314–0.783 g/cm^3;(8)
Light magnesium carbonate: ≈0.21 g/cm^3.

Density (true): Heavy magnesium carbonate: 1.966–2.261 g/cm^3(8)

Moisture content: at relative humidities between 15% and 65% the equilibrium moisture content of heavy magnesium carbonate at 25°C is about 1% w/w; at relative humidities above 75% the equilibrium moisture content at 25°C is about 5% w/w.(3)

Particle size distribution:
Heavy magnesium carbonate: 7–43 μm median particle size(8)
Light magnesium carbonate: 99.95% through a 44.5 μm (#350 mesh) sieve for light magnesium carbonate.

Solubility: practically insoluble in water but soluble in water containing carbon dioxide. Insoluble in ethanol (95%) and other solvents. Magnesium carbonate dissolves and effervesces on contact with dilute acids.

Specific surface area:
7.8–18.2 m^2/g for granular heavy magnesium carbonate;
4.4–15.5 m^2/g for spray-dried heavy magnesium carbonate;(3)
14.64–14.78 m^2/g for basic heavy magnesium carbonate.

11 Stability and Storage Conditions

Magnesium carbonate is stable in dry air and on exposure to light. The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatible with phenobarbital sodium,(4,9) diazepam solution at a pH ⩾5,(10) some binary powder mixtures,(11) lansoprazole,(5) and formaldehyde.(12) Acids will dissolve magnesium carbonate, with the liberation of carbon dioxide. Slight alkalinity is imparted to water. Magnesium carbonate was also found to increase the dissolution of acetazolamide formulations at a pH of 1.12; however, dissolution was retarded at a pH of 7.4.(6)

13 Method of Manufacture

Depending upon the manufacturing process used, the composition of the magnesium carbonate obtained may vary from normal hydrated magnesium carbonate to basic hydrated magnesium carbonate.

Light magnesium carbonate may be manufactured by saturating an aqueous suspension of dolomite, $CaMg(CO_3)_2$, with carbon dioxide under pressure. On increase of the temperature, calcium carbonate precipitates almost entirely. The filtered solution is then heated to boiling; the magnesium bicarbonate in the solution loses carbon dioxide and water, and light magnesium carbonate precipitates.

Heavy magnesium carbonate may be manufactured by mixing a hot concentrated solution of magnesium chloride or magnesium sulfate with a solution of sodium carbonate. The heavy magnesium carbonate may be either precipitated to produce a granular material or spray-dried. Varying the temperature of the reaction solutions produces heavy magnesium carbonate with differing physical properties: e.g., material with a higher specific surface area is produced at a lower reaction temperature. Low processing temperature provided the largest surface area, which produced optimum granules or spray-dried powder.(3) If dilute magnesium chloride or magnesium sulfate solutions are used for the reaction, a less dense material is produced.

Magnesium carbonates in varying states of hydration are also found as minerals in nature.

14 Safety

Magnesium carbonate is used as an excipient in oral solid-dosage pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material. However, the use of magnesium salts, such as magnesium carbonate, is contraindicated in patients with renal impairment. In addition, the probable oral lethal dose in humans has been estimated at 0.5–5.0 g/kg body weight.(12)

On contact with gastric acid, magnesium carbonate reacts in the stomach to form soluble magnesium chloride and carbon dioxide. Magnesium carbonate should therefore not be used as an antacid by those individuals whose stomachs cannot tolerate the evolution of carbon dioxide. Some magnesium is absorbed but is usually excreted in the urine. As with other magnesium salts, magnesium carbonate has a laxative effect and may cause diarrhea.

Therapeutically, the usual dose of magnesium carbonate as an antacid is 250–500 mg, and 2.0–5.0 g as a laxative.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Magnesium carbonate may be irritant to the eyes; eye protection is recommended. OSHA standards state that IPA 8-hour time weighted airborne average is 10 mg/m^3.(12)

16 Regulatory Acceptance

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Magnesium carbonate anhydrous; magnesium carbonate hydroxide; normal magnesium carbonate.

Magnesium carbonate anhydrous

Empirical formula: $MgCO_3$
Molecular weight: 84.31
CAS number: [546-93-0]
Synonyms: carbonic acid, magnesium salt anhydrous (1 : 1); E504; magnesite.
Appearance: odorless, white-colored bulky powder or light, friable masses.
Melting point: decomposes at 350°C.

Magnesium carbonate hydroxide

Empirical formula: $(MgCO_3)_4 \cdot Mg(OH)_2 \cdot 5H_2O$
Molecular weight: 485.65
CAS number: [39409-82-0]
Synonyms: carbonic acid, magnesium salt (1 : 1), mixture with magnesium hydroxide and magnesium hydrate; dypingite; E504.
Appearance: odorless, white-colored bulky powder or light, friable masses.
Melting point: on heating at 700°C it is converted into magnesium oxide.
Specific gravity: 1.45
Comments: the EINECS number for magnesium carbonate hydroxide is 235-192-7.

Normal magnesium carbonate

Empirical formula: $MgCO_3 \cdot xH_2O$
CAS number: [23389-33-5]
Synonyms: carbonic acid, magnesium salt (1 : 1), hydrate; magnesium carbonate, normal hydrate; E504.
Appearance: odorless, white-colored bulky powder or light, friable masses.

18 Comments

Magnesium carbonate has been found to increase the dissolution of acetazolamide formulations at a pH of 1.12; however, dissolution was retarded at a pH of 7.4.(6) Magnesium carbonate has also been shown to alter the pharmacokinetics of halofantrine, increasing the time to reach maximum plasma concentration and reducing maximum plasma concentrations.(13) Because drug interactions can occur with a variety of antacids,(14) the potential for these effects should be considered when designing pharmaceutical formulations containing magnesium carbonate.

A specification for magnesium carbonate is contained in the Food Chemicals Codex (FCC). The EINECS number for magnesium carbonate is 208-915-9.

19 Specific References

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21 Authors

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22 Date of Revision

7 June 2005.

Magnesium Oxide

1 Nonproprietary Names

BP: Heavy magnesium oxide and Light magnesium oxide
JP: Magnesium oxide
PhEur: Magnesii oxidum ponderosum (Magnesium oxide, heavy) and Magnesii oxidum leve (Magnesium oxide, light)
USP: Magnesium oxide
See Section 8.

2 Synonyms

Calcined magnesia; calcinated magnesite; *Destab*; E530; *Magcal*; *Magchem 100*; *Maglite*; magnesia; magnesia monoxide; magnesia usta; *Magnyox*; *Marmag*; *Oxymag*; periclase.

3 Chemical Name and CAS Registry Number

Magnesium oxide [1309-48-4]

4 Empirical Formula and Molecular Weight

MgO 40.30

5 Structural Formula

MgO

6 Functional Category

Anticaking agent; emulsifying agent; glidant; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Magnesium oxide is used as an alkaline diluent in solid-dosage forms to modify the pH of tablets.(1) It can be added to solid-dosage forms to bind excess water and keep the granulation dry. In combination with silica, magnesium oxide can be used as an auxiliary glidant.(2) It is also used as a food additive and as an antacid, either alone or in conjunction with aluminum hydroxide. Magnesium oxide is additionally used as an osmotic laxative and a magnesium supplement to treat deficiency states.

8 Description

Two forms of magnesium oxide exist: a bulky form termed light magnesium oxide and a dense form termed heavy magnesium oxide. The USP 28 defines both forms in a single monograph, while other pharmacopeias have separate monographs for each form. For the heavy variety, 5 g occupies a volume of about 10–20 mL; for the light variety, 5 g occupies a volume of about 40–50 mL as defined by the USP 28.

Both forms of magnesium oxide occur as fine, white, odorless powders. They possess a cubic crystal structure.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for magnesium oxide.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Loss on ignition	⩽10.0%	⩽8.0%	⩽10.0%
Color of solution	—	+	—
Free alkali and soluble salts	+	—	⩽2.0%
Soluble substances	—	⩽2.0%	—
Acid-insoluble substances	⩽0.1%	⩽0.1%	⩽0.1%
Arsenic	⩽10 ppm	⩽4 ppm	—
Calcium	—	⩽1.5%	⩽1.1%
Calcium oxide	+	—	—
Carbonate	+	—	—
Heavy metals	⩽40 ppm	⩽30 ppm	⩽20 µg/g
Iron	⩽500 ppm	+	⩽0.05%
Heavy magnesium oxide	—	⩽0.07%	—
Light magnesium oxide	—	⩽0.1%	—
Chloride	—	+	—
Heavy magnesium oxide	—	⩽0.1%	—
Light magnesium oxide	—	⩽0.15%	—
Fluoride	⩽0.08%	—	—
Sulfate	—	⩽1.0%	—
Assay	⩾96.0%	98.0–100.5%	96.0–100.5%

10 Typical Properties

Acidity/alkalinity: pH = 10.3 (saturated aqueous solution)
Boiling point: 3600°C
Melting point: 2800°C
Particle size distribution: 99.98% less than 45 µm in size (light magnesium oxide).
Refractive index: 1.735
Solubility: soluble in dilute acids and ammonium salt solutions; very slightly soluble in pure water (solubility is increased by carbon dioxide); practically insoluble in ethanol (95%).
Specific gravity: 3.581 g/cm^3 at 25°C

11 Stability and Storage Conditions

Magnesium oxide is stable at normal temperatures and pressures. However, it forms magnesium hydroxide in the presence of water. Magnesium oxide is hygroscopic and rapidly absorbs water and carbon dioxide on exposure to the air, the light form more readily than the heavy form.

The bulk material should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Magnesium oxide is a basic compound and as such can react with acidic compounds in the solid state to form salts such as $Mg(ibuprofen)_2$ or degrade alkaline-labile drugs.(3) Adsorption of various drugs onto magnesium oxide has been reported, such as antihistamines,(4) antibiotics (especially tetracyclines),(5) salicylates,(6) atropine sulfate,(7) hyoscyamine hydrobromide,(7) paracetamol, chloroquine,(8) and anthranilic acid derivatives have been reported to adsorb onto the surface of magnesium oxide.(9) Magnesium oxide can also complex with polymers, e.g. *Eudragit RS*, to retard drug release(10–12) and can interact in the solid state with phenobarbitone sodium.(13) Magnesium oxide can also reduce the bioavailability of phenytoin,(14) trichlormethiazide,(15) and anti-arrhythmics.(16) The presence of magnesium oxide can also have a negative impact on the solid-state chemical stability of drugs, such as diazepam.(17)

13 Method of Manufacture

Magnesium oxide occurs naturally as the mineral periclase. It can be manufactured by many processes. Limestone containing the mineral dolomite is calcinated at high temperatures to produce dolime, which then reacts with magnesium chloride-rich sea water to produce magnesium hydroxide and calcium chloride.(18) The magnesium hydroxide is then calcinated to produce magnesium oxide and water. In another process, mined magnesite ($MgCO_3$) is calcinated to produce magnesium oxide and carbon dioxide.(18) Purification methods include crushing and size separation, heavy-media separation, and froth flotation. Producing magnesium oxide from sea water is a process that involves heating magnesium chloride concentrated brine from the Dead Sea. The magnesium chloride decomposes into magnesium oxide and hydrochloric acid.(18) Magnesium oxide may also be produced by the thermal decomposition of magnesium chloride, magnesium sulfate, magnesium sulfite, nesquehonite, and the basic carbonate $5MgO{\cdot}4CO_2{\cdot}5H_2O$. Purification of the magnesium oxide produced through thermal degradation is carried out by filtration or sedimentation.

14 Safety

Magnesium oxide is widely used in oral formulations as an excipient and as a therapeutic agent. Therapeutically, 250–500 mg is administered orally as an antacid and 2–5 g as an osmotic laxative. Magnesium oxide is generally regarded as a nontoxic material when employed as an excipient, although adverse effects, due to its laxative action, may occur if high doses are ingested orally.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Magnesium oxide may be harmful if inhaled, ingested, or absorbed through the skin in quantity and is irritating to the eyes and respiratory system. Gloves, eye protection, and a dust mask or respirator are recommended. In the US and UK, the long-term (8-hour TWA) occupational exposure limits for magnesium oxide, calculated as magnesium, are 10 mg/m^3 for total dust and 4 mg/m^3 for respirable dust.(18,19) The short-term (15-minute) limit for respirable dust is 10 mg/m^3.(18,19)

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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18 Comments

A specification for magnesium oxide is contained in the Food Chemicals Codex (FCC). The EINECS number for magnesium oxide is 215-171-9.

19 Specific References

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JT Colvin.

22 Date of Revision

26 April 2005.

Magnesium Silicate

1 Nonproprietary Names

JP: Magnesium silicate
USPNF: Magnesium silicate

2 Synonyms

E553a; synthetic magnesium silicate.

3 Chemical Name and CAS Registry Number

Silicic acid, magnesium salt [1343-88-0]

4 Empirical Formula and Molecular Weight

$MgO\cdot SiO_2\cdot xH_2O$

See also Sections 5 and 17.

5 Structural Formula

Magnesium silicate is a compound of magnesium oxide and silicon dioxide. *See also* Section 17.

The JP 2001 states that magnesium silicate contains not less than 45.0% of silicon dioxide (SiO_2: molecular weight 60.08) and not less than 20.0% of magnesium oxide (MgO: 40.30), and the ratio of percentage (%) of magnesium oxide to silicon dioxide is not less than 2.2 and not more than 2.5.

The USPNF 23 describes magnesium silicate as a compound of magnesium oxide (MgO) and silicon dioxide (SiO_2) that contains not less than 15.0% of MgO and not less than 67.0% of SiO_2 calculated on the ignited basis.

6 Functional Category

Anticaking agent; glidant.

7 Applications in Pharmaceutical Formulation or Technology

Magnesium silicate is used in oral pharmaceutical formulations and food products as a glidant and an anticaking agent.

8 Description

Magnesium silicate occurs as an odorless and tasteless, fine, white-colored powder that is free from grittiness.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for magnesium silicate.

Test	JP 2001	USPNF 23
Identification	+	+
pH (10% aqueous suspension)	—	7.0–10.8
Loss on drying	—	⩽15%
Soluble salts	⩽0.02 g	⩽3.0%
Chloride	⩽0.053%	—
Free alkali	+	+
Heavy metals	⩽30 ppm	⩽20 μg/g
Arsenic	⩽5 ppm	—
Sulfate	⩽0.48%	—
Organic volatile impurities	—	+
Loss on ignition	⩽34%	⩽15%
Fluoride	—	⩽10 ppm
Lead	—	⩽0.001%
Acid-consuming capacity	+	—
Ratio of SiO_2 to MgO	2.2–2.5	2.5–4.5
Assay for MgO	⩾20.0%	⩾15%
Assay for SiO_2	⩾45.0%	⩾67%

10 Typical Properties

Moisture content: magnesium silicate is slightly hygroscopic.

Solubility: practically insoluble in ethanol (95%), ether, and water.

11 Stability and Storage Conditions

Magnesium silicate should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Magnesium silicate may decrease the oral bioavailability of drugs such as mebeverine hydrochloride,(1) sucralfate, and tetracycline, via chelation or binding, when they are taken together. The dissolution rate of folic acid,(2) erythromycin stearate,(3) paracetamol,(4) and chloroquine phosphate,(4) may be retarded by adsorption onto magnesium silicate. Antimicrobial preservatives, such as parabens, may be inactivated by the addition of magnesium silicate.(5)

Magnesium silicate is readily decomposed by mineral acids.

13 Method of Manufacture

Magnesium silicate may be prepared from sodium silicate and magnesium sulfate. The silicate also occurs in nature as the minerals meerschaum, parasepiolite, and sepiolite.

14 Safety

Magnesium silicate is used in oral pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material.

Orally administered magnesium silicate is neutralized in the stomach to form magnesium chloride and silicon dioxide; some magnesium is absorbed. Caution should be used when greater than 50 mEq of magnesium is given daily to persons with impaired renal function, owing to the risk of hypermagnesemia.

Reported adverse effects include the formation of bladder and renal calculi following the regular use, for many years, of magnesium silicate as an antacid.(6,7)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended.

16 Regulatory Acceptance

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Magnesium aluminum silicate; magnesium metasilicate; magnesium orthosilicate; magnesium trisilicate; talc.

Magnesium metasilicate

Comments: magnesium metasilicate ($MgSiO_3$) occurs in nature as the minerals clinoenstatite, enstatite, and protoenstatite.

Magnesium orthosilicate

Comments: magnesium orthosilicate (Mg_2SiO_4) occurs in nature as the mineral forsterite.

18 Comments

A specification for magnesium silicate is contained in the Food Chemicals Codex (FCC). The EINECS number for magnesium silicate is 215-681-1.

19 Specific References

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21 Authors

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22 Date of Revision

8 August 2005.

Magnesium Stearate

1 Nonproprietary Names

BP: Magnesium stearate
JP: Magnesium stearate
PhEur: Magnesii stearas
USPNF: Magnesium stearate

2 Synonyms

Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.

3 Chemical Name and CAS Registry Number

Octadecanoic acid magnesium salt [557-04-0]

4 Empirical Formula and Molecular Weight

$C_{36}H_{70}MgO_4$ 591.34

The USPNF 23 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$). The PhEur 2005 describes magnesium stearate as a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid and palmitic acid and in minor proportions other fatty acids.

5 Structural Formula

$[CH_3(CH_2)_{16}COO]_2Mg$

6 Functional Category

Tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams. *See also* Section 18.

8 Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for magnesium stearate.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Microbial limits	+	+	+
Aerobic microbes	≤1000/g	≤10^3/g	≤10^3/g
Fungi and yeasts	≤500/g	—	≤500/g
Acidity or alkalinity	+	+	+
Acid value of the fatty acid	—	195–210	—
Freezing point	—	≥53°C	—
Nickel	—	≤5 ppm	—
Cadmium	—	≤3 ppm	—
Specific surface area	—	—	+
Loss on drying	≤6.0%	≤6.0%	≤6.0%
Chloride	≤0.1%	≤0.1%	≤0.1%
Sulfate	≤1.0%	≤0.5%	≤1.0%
Lead	—	≤10 ppm	≤0.001%
Heavy metals	≤20 ppm	—	—
Relative stearic/palmitic content	+	+	+
Organic volatile impurities	—	—	+
Assay (dried, as Mg)	4.0–5.0%	4.0–5.0%	4.0–5.0%

10 Typical Properties

Crystalline forms: high-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.
Density (bulk): 0.159 g/cm^3
Density (tapped): 0.286 g/cm^3
Density (true): 1.092 g/cm^3
Flash point: 250°C
Flowability: poorly flowing, cohesive powder.
Melting range:
117–150°C (commercial samples);
126–130°C (high purity magnesium stearate).
Solubility: practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).
Specific surface area: 1.6–14.8 m^2/g

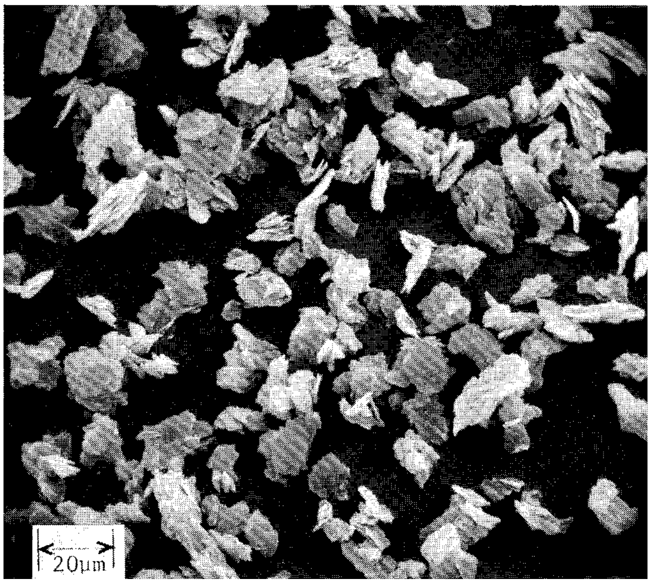
11 Stability and Storage Conditions

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

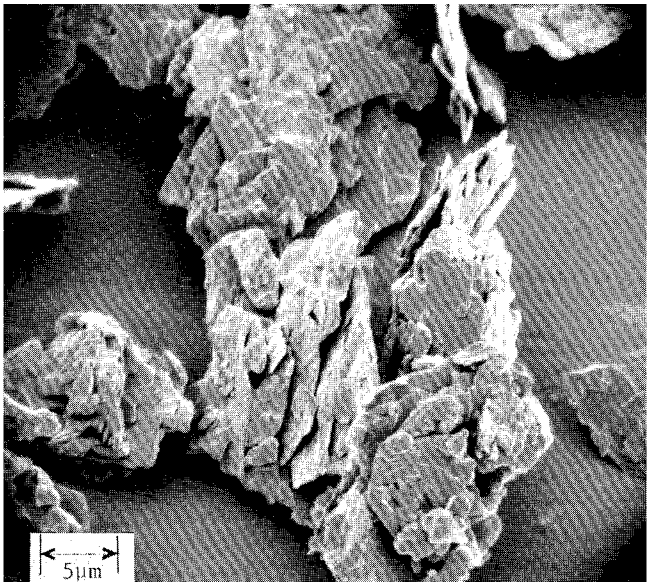
12 Incompatibilities

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

SEM: 1
Excipient: Magnesium stearate
Magnification: 600×



SEM: 2
Excipient: Magnesium stearate
Magnification: 2400×



13 Method of Manufacture

Magnesium stearate is prepared either by the interaction of aqueous solutions of magnesium chloride with sodium stearate or by the interaction of magnesium oxide, hydroxide, or carbonate with stearic acid at elevated temperatures.

14 Safety

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation.

No toxicity information is available relating to normal routes of occupational exposure. Limits for heavy metals in magnesium stearate have been evaluated in terms of magnesium stearate worst-case daily intake and heavy metal composition.(1)

Toxicity assessments of magnesium stearate in rats have indicated that it is not irritating to the skin, and is nontoxic when administered orally or inhaled.(2,3)

Magnesium stearate has not been shown to be carcinogenic when implanted into the bladder of mice.(4)

LD_{50} (rat, inhalation): >2 mg/L(2)
LD_{50} (rat, oral): >10 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing, and choking. Magnesium stearate should be handled in a well-ventilated environment; a respirator is recommended.

16 Regulatory Acceptance

GRAS listed. Accepted as a food additive in the UK. Included in the FDA Inactive Ingredients Guide (oral capsules, powders, and tablets; buccal and vaginal tablets; topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Calcium stearate; magnesium aluminum silicate; stearic acid; zinc stearate.

18 Comments

Magnesium stearate is hydrophobic and may retard the dissolution of a drug from a solid dosage form; the lowest possible concentration is therefore used in such formulations.(5–10) Capsule dissolution is also sensitive to both the amount of magnesium stearate in the formulation and the mixing time; higher levels of magnesium stearate and long mixing times can result in the formation of hydrophobic powder beds that do not disperse after the capsule shell dissolves.(11,12)

An increase in the coefficient of variation of mixing and a decrease in the dissolution rate have been observed following blending of magnesium stearate with a tablet granulation. Tablet dissolution rate and crushing strength decreased as the time of blending increased; and magnesium stearate may also increase tablet friability. Blending times with magnesium stearate should therefore be carefully controlled.(13–29)

The existence of various crystalline forms of magnesium stearate has been established.(30–34) A trihydrate, a dihydrate, and an anhydrate have been isolated,(5,32,33,35) and an amorphous form has been observed.(36) While the hydrate forms are stable in the presence of moisture, the anhydrous form adsorbs moisture at relative humidity up to 50%, and at higher humidities rehydrates to form the trihydrate. The anhydrate can be formed by drying either of the hydrates at 105°C.(33)

It has not been conclusively established which form of pure magnesium stearate possesses the best lubricating properties.(31,32,36,37) Commercial lots of magnesium stearate generally consist of mixtures of crystalline forms.(32,34,36–40) Because of the possibility of conversion of crystalline forms during heating, consideration should be given to the pretreatment conditions employed when determining physical properties of magnesium stearate powders such as surface area.(41)

Physical properties of magnesium stearate can vary among batches from different manufacturers(40) because the solid-state characteristics of the powder are influenced by manufacturing variables.(31) Variations in the physical properties of different lots of magnesium stearate from the same vendor have also been observed.(40) Presumably because of these variations, it has not been possible to conclusively correlate the dissolution rate retardation with observed lubricity.(42)

However, various physical properties of different batches of magnesium stearate such as specific surface area, particle size, crystalline structure, moisture content, and fatty acid composition have been correlated with lubricant efficacy.(32,36,39,40,43–47) Due to variations in the specific surface area, the USPNF 23 labeling states that specific surface area and the method specified for its determination should be listed on the label. Reduction in dissolution caused by the effects of magnesium stearate in some cases can be overcome by including a highly swelling disintegrant in the formulation.(48)

There is evidence to suggest that the hydrophobic nature of magnesium stearate can vary from batch to batch owing to the presence of water-soluble, surface-active impurities such as sodium stearate. Batches containing very low concentrations of these impurities have been shown to retard the dissolution of a drug to a greater extent than when using batches that contain higher levels of impurities.(42) One study related lubricity to the fatty acid composition (stearate : palmitate) of lubricant lots for tablet formulations based on compaction data and tablet material properties.(47) However, other studies have indicated that fatty acid composition has no influence on lubricant activity(32) and high-purity magnesium stearate was as effective a lubricant as the commercial material.(10) Moisture sorption at different relative humidities can result in morphological changes in the magnesium stearate.(49,50)

A specification for magnesium stearate is included in the Food Chemicals Codex (FCC). The EINECS number for magnesium stearate is 209-150-3.

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21 Authors

LV Allen, PE Luner.

22 Date of Revision

9 August 2005.

Magnesium Trisilicate

1 Nonproprietary Names

BP: Magnesium trisilicate
PhEur: Magnesii trisilicas
USP: Magnesium trisilicate

2 Synonyms

E553(a); magnesium mesotrisilicate; silicic acid, magnesium salt (1 : 2), hydrate.

3 Chemical Name and CAS Registry Number

Magnesium trisilicate [14987-04-3]

4 Empirical Formula and Molecular Weight

$Mg_2Si_3O_8 \cdot xH_2O$ 260.86 (anhydrous)

5 Structural Formula

$2MgO \cdot 3SiO_2 \cdot xH_2O$

6 Functional Category

Anticaking agent; glidant; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Magnesium trisilicate is used in oral pharmaceutical formulations and food products as a glidant. It is also used therapeutically as an antacid, and also for the treatment of ciprofloxacin overdose or toxicity.(1)

8 Description

The USP 28 describes magnesium trisilicate as a compound of magnesium oxide and silicon dioxide with varying proportions of water. It contains not less than 20% of magnesium oxide and not less than 45% of silicon dioxide. The PhEur 2005 similarly describes magnesium trisilicate as having a variable composition corresponding to the approximate formula $Mg_2Si_3O_8 \cdot xH_2O$. It contains not less than 29% of magnesium oxide and not less than the equivalent of 65% of silicon dioxide, both calculated with reference to the ignited substance.

Magnesium trisilicate occurs as an odorless and tasteless, fine, white-colored powder that is free from grittiness.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for magnesium trisilicate.

Test	PhEur 2005	USP 28
Identification	+	+
Ratio of SiO_2 to MgO	—	2.10–2.37
Loss on ignition	17.0–34.0%	17.0–34.0%
Water-soluble salts	⩽1.5%	⩽1.5%
Chloride	⩽500 ppm	⩽0.055%
Sulfates	⩽0.5%	⩽0.5%
Alkalinity	+	+
Arsenic	⩽4 ppm	⩽8 ppm
Heavy metals	⩽40 ppm	⩽0.003%
Acid-absorbing capacity	⩽100.0 mL	140–160 mL
Assay of MgO	⩾29.0%(a)	⩾20.0%
Assay of SiO_2	⩾65.0%(a)	⩾45.0%

(a) With reference to the ignited substance.

10 Typical Properties

Moisture content: magnesium trisilicate is slightly hygroscopic. At relative humidities of 15–65%, the equilibrium moisture content at 25°C is 17–23% w/w; at relative humidities of 75–95%, the equilibrium moisture content is 24–30% w/w.

Solubility: practically insoluble in diethyl ether, ethanol (95%) and water.

11 Stability and Storage Conditions

Magnesium trisilicate is stable if stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Magnesium trisilicate, when taken with drugs such as mebeverine hydrochloride,(2) proguanil,(3) norfloxacin,(4) sucralfate, and tetracycline, may cause a reduction in bioavailability via binding or chelation. The dissolution rate of folic acid,(5) erythromycin stearate,(6) paracetamol, and chloroquine phosphate(7) may be retarded by adsorption onto magnesium trisilicate. Antimicrobial preservatives, such as the parabens, may be inactivated by the addition of magnesium trisilicate.(8)

Magnesium trisilicate is also readily decomposed by mineral acids.

13 Method of Manufacture

Magnesium trisilicate may be prepared from sodium silicate and magnesium sulfate. It also occurs in nature as the minerals meerschaum, parasepiolite, and sepiolite.

14 Safety

Magnesium trisilicate is used in oral pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material.

When administered orally, magnesium trisilicate is neutralized in the stomach to form magnesium chloride and silicon dioxide; some magnesium may be absorbed. Caution should be used when concentrations greater than 50 mEq of magnesium are given daily to persons with impaired renal function, owing to the risk of hypermagnesemia.

Therapeutically, up to about 2 g of magnesium trisilicate may be taken daily as an antacid.

Reported adverse effects include the potential for osmotic diarrhea in the elderly using antacids containing magnesium trisilicate;(9) and the potential for the formation of bladder and renal calculi following the long-term use of magnesium trisilicate as an antacid.(10,11)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Calcium silicate; magnesium aluminum silicate; magnesium silicate; magnesium trisilicate anhydrous; talc.

Calcium silicate

Appearance: white to off-white-colored, free-flowing powder that remains free-flowing after absorbing relatively large amounts of water or other liquids.

Solubility: practically insoluble in water. Forms a gel with mineral acids.

Handling precautions: in the UK, the long-term (8-hour TWA) occupational exposure standards for calcium silicate are 10 mg/m^3 for total inhalable dust and 4 mg/m^3 for respirable dust.(12)

Comments: many different forms of calcium silicate are known such as $CaSiO_3$, Ca_2SiO_4, and Ca_3SiO_5. Usually these occur in the hydrated form and contain varying amounts of water of crystallization. Calcium silicate is used in pharmaceutical formulations as a glidant and anticaking agent.(13) Also used in food products (GRAS listed). The EINECS number for calcium silicate is 215-710-8.

Magnesium trisilicate anhydrous

Empirical formula: $Mg_2Si_3O_8$
Molecular weight: 260.86
CAS number: [14987-04-3]

18 Comments

Magnesium trisilicate is regarded as a type of magnesium silicate. The EU food additive code E553(a) has been applied to both. The EINECS number for magnesium trisilicate is 239-076-7.

19 Specific References

1 Ofoefule SI, Okonta M. Adsorption studies of ciprofloxacin: evaluation of magnesium trisilicate, kaolin and starch as alternatives for the management of ciprofloxacin poisoning. *Boll Chim Farm* 1999; **138**: 239–242.
2 Al-Gohary OMN. An *in vitro* study of the interaction between mebeverine hydrochloride and magnesium trisilicate powder. *Int J Pharm* 1991; **67**: 89–95.
3 Onyeji CO, Babalola CP. The effect of magnesium trisilicate on proguanil absorption. *Int J Pharm* 1993; **100**: 249–252.
4 Okhamafe AO, Akerele JO, Chukuka CS. Pharmacokinetic interactions of norfloxacin with some metallic medicinal agents. *Int J Pharm* 1991; **68**: 11–18.
5 Iwuagwu MA, Jideonwo A. Preliminary investigations into the in-vitro interaction of folic acid with magnesium trisilicate and edible clay. *Int J Pharm* 1990; **65**: 63–67.
6 Arayne MS, Sultana N. Erythromycin–antacid interaction. *Pharmazie* 1993; **48**: 599–602.
7 Iwuagwu MA, Aloko KS. Adsorption of paracetamol and chloroquine phosphate by some antacids. *J Pharm Pharmacol* 1992; **44**(8): 655–658.
8 Allwood MC. The adsorption of esters of *p*-hydroxybenzoic acid by magnesium trisilicate. *Int J Pharm* 1982; **11**: 101–107.
9 Ratnaike RN, Jones TE. Mechanisms of drug-induced diarrhoea in the elderly. *Drugs & Aging* 1998; **13**: 245–253.
10 Joekes AM, Rose GA, Sutor J. Multiple renal silica calculi. *Br Med J* 1973; **1**: 146–147.
11 Levison DA, Crocker PR, Banim S, Wallace DMA. Silica stones in the urinary bladder. *Lancet* 1982; I: 704–705.
12 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.
13 Asano T, Tsubuku S, Sugawara S, *et al*. Changes in volume and compression energy upon compression of calcium silicate tablets. *Drug Dev Ind Pharm* 1997; **23**: 679–685.

20 General References

Anonymous. The silicates: attapulgite, kaolin, kieselguhr, magnesium trisilicate, pumice, talc. *Int J Pharm Compound* 1998; **2**(2): 162–163.

21 Authors

AS Kearney.

22 Date of Revision

19 August 2005.

Malic Acid

1 Nonproprietary Names

PhEur: Acidum malicum
USPNF: Malic acid

2 Synonyms

Apple acid; E296; 2-hydroxy-1,4-butanedioic acid; hydroxybutanedioic acid; 1-hydroxy-1,2-ethanedicarboxylic acid; hydroxysuccinic acid; 2-hydroxysuccinic acid; DL-malic acid.

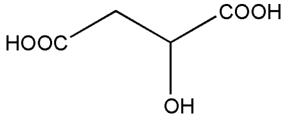
3 Chemical Name and CAS Registry Number

Hydroxybutanedioic acid [6915-15-7]
(*RS*)-(±)-Hydroxybutanedioic acid [617-48-1]

4 Empirical Formula and Molecular Weight

$C_4H_6O_5$ 134.09

5 Structural Formula



6 Functional Category

Acidulant; antioxidant; chelating and buffering agent; flavoring agent; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Malic acid is used in pharmaceutical formulations as a general-purpose acidulant. It possesses a slight apple flavor and is used as a flavoring agent to mask bitter tastes and provide tartness. Malic acid is also used as an alternative to citric acid in effervescent powders, mouthwashes, and tooth-cleaning tablets.

In addition, malic acid has chelating and antioxidant properties. It may be used with butylated hydroxytoluene as a synergist in order to retard oxidation in vegetable oils. In food products it may be used in concentrations up to 420 ppm.

Therapeutically, malic acid has been used topically in combination with benzoic acid and salicylic acid to treat burns, ulcers, and wounds. It has also been used orally and parenterally, either intravenously or intramuscularly, in the treatment of liver disorders, and as a sialagogue.(1)

8 Description

White or nearly white, crystalline powder or granules having a slight odor and a strongly acidic taste. It is hygroscopic. The synthetic material produced commercially in Europe and the USA is a racemic mixture, whereas the naturally occurring material found in apples and many other fruits and plants is levorotatory.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for malic acid.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Residue on ignition	⩽0.1%	⩽0.1%
Appearance of solution	+	—
Water-insoluble substances	⩽0.1%	⩽0.1%
Heavy metals	⩽20 ppm	⩽0.002%
Fumaric acid	—	⩽0.1%
Maleic acid	—	⩽0.05%
Optical rotation	–0.1° to +0.1°	—
Organic volatile impurities	—	+
Related substances	+	—
Water	⩽2.0%	—
Assay	99.0–101.0%	99.0–100.5%

10 Typical Properties

Data shown below are for the racemate. *See* Section 17 for other data for the D- and L- forms.

Acidity/alkalinity: pH = 2.35 (1% w/v aqueous solution at 25°C)

Boiling point: 150°C (with decomposition)

Density (bulk): 0.81 g/cm^3

Density (tapped): 0.92 g/cm^3

Dissociation constant:
pK_{a1} = 3.40 at 25°C;
pK_{a2} = 5.05 at 25°C.

Melting point: 131–132°C

Solubility: freely soluble in ethanol (95%) and water but practically insoluble in benzene. A saturated aqueous solution contains about 56% malic acid at 20°C. *See* Table II.

Table II: Solubility of malic acid.

Solvent	Solubility at 20°C
Acetone	1 in 5.6
Diethyl ether	1 in 119
Ethanol (95%)	1 in 2.6
Methanol	1 in 1.2
Propylene glycol	1 in 1.9
Water	1 in 1.5–2.0

Specific gravity:
1.601 at 20°C;
1.250 (saturated aqueous solution at 25°C).

Viscosity (dynamic): 6.5 mPa s (6.5 cP) for a 50% w/v aqueous solution at 25°C.

11 Stability and Storage Conditions

Malic acid is stable at temperatures up to 150°C. At temperatures above 150°C it begins to lose water very slowly to yield fumaric acid; complete decomposition occurs at about 180°C to give fumaric acid and maleic anhydride.

Malic acid is readily degraded by many aerobic and anaerobic microorganisms. Conditions of high humidity and elevated temperatures should be avoided to prevent caking.

The effects of grinding and humidity on malic acid have also been investigated.(2)

The bulk material should be stored in a well-closed container, in a cool, dry place.

12 Incompatibilities

Malic acid can react with oxidizing materials. Aqueous solutions are mildly corrosive to carbon steels.

13 Method of Manufacture

Malic acid is manufactured by hydrating maleic and fumaric acids in the presence of suitable catalysts. The malic acid formed is then separated from the equilibrium product mixture.

14 Safety

Malic acid is used in oral, topical, and parenteral pharmaceutical formulations in addition to food products, and is generally regarded as a relatively nontoxic and nonirritant material. However, concentrated solutions may be irritant.

LD_{50} (rat, oral): 1.6 g/kg(3)
LD_{50} (rat, IP): 0.1 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Malic acid, and concentrated malic acid solutions may be irritant to the skin, eyes, and mucous membranes. Gloves and eye protection are recommended.

16 Regulatory Status

GRAS listed. Both the racemic mixture and the levorotatory isomer are accepted as food additives in Europe. The DL- and L-forms are included in the FDA Inactive Ingredients Guide (oral preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Citric acid; fumaric acid; D-Malic acid; -Malic acid; tartaric acid.

D-Malic acid

Empirical formula: $C_4H_6O_5$
Molecular weight: 134.09
CAS number: [636-61-3]
Synonyms: (*R*)-(+)-hydroxybutanedioic acid; D-(+)-malic acid.
Melting point: 99–101°C
Specific rotation $[\alpha]_D^{20}$: +5.2° (in acetone at 18°C).

L-Malic acid

Empirical formula: $C_4H_6O_5$
Molecular weight: 134.09
CAS number: [97-67-6]
Synonyms: apple acid; (*S*)-(–)-hydroxybutanedioic acid; L-(–)-malic acid.
Boiling point: ≈140°C (with decomposition)
Melting point: 99–100°C
Solubility: practically insoluble in benzene. *See also* Table III.

Table III: Solubility of L-malic acid

Solvent	Solubility at 20°C
Acetone	1 in 1.6
Diethyl ether	1 in 37
Dioxane	1 in 1.3
Ethanol (95%)	1 in 1.2
Methanol	1 in 0.51
Water	1 in 2.8

Specific gravity: 1.595 at 20°C
Specific rotation $[\alpha]_D^{20}$: –5.7° (in acetone at 18°C)

18 Comments

A specification for malic acid is contained in the Food Chemical Codex (FCC). The EINECS number for malic acid is 202-601-5.

19 Specific References

1 Sweetman SC, ed. *Martindale: The Complete Drug Reference,* 34th edn. London: Pharmaceutical Press, 2005: 1709.
2 Piyarom S, Yonemochi E, Oguchi T, Yamamoto K. Effects of grinding and humidification on the transformation of conglomerate to racemic compound in optically active drugs. *J Pharm Pharmacol* 1997; **49**: 384–389.
3 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 2273.

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Anonymous. Malic and fumaric acids. *Manuf Chem Aerosol News* 1964; **35**(12): 56–59.
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21 Authors

SC Owen.

22 Date of Revision

12 August 2005.

Maltitol

1 Nonproprietary Names

BP: Maltitol
PhEur: Maltitolum

2 Synonyms

Amalty; *C*PharmMaltidex*; E965; hydrogenated maltose; *Malbit*; *Maltisorb*; *Maltit*; D-maltitol.

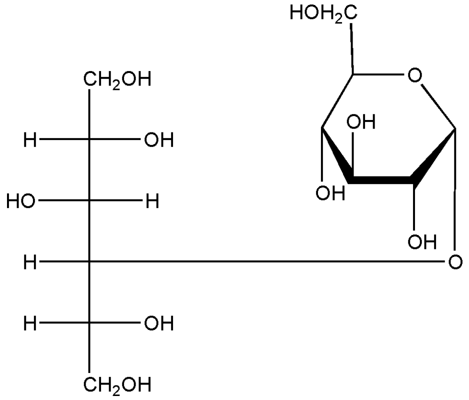
3 Chemical Name and CAS Registry Number

4-O-α-D-Glucopyranosyl-D-glucitol [585-88-6]

4 Empirical Formula and Molecular Weight

$C_{12}H_{24}O_{11}$ 344.32

5 Structural Formula



6 Functional Category

Coating agent; diluent; granulating agent; sweetening agent.

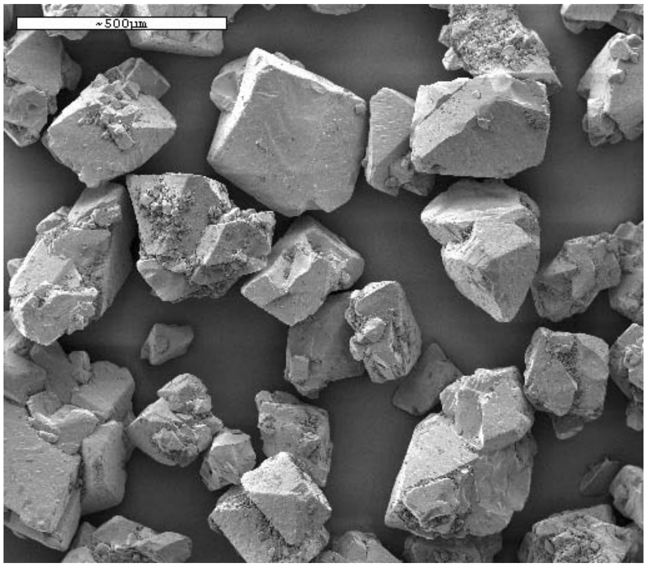
7 Applications in Pharmaceutical Formulation or Technology

Maltitol is widely used in the pharmaceutical industry in the formulation of oral dosage forms. It is a noncariogenic bulk sweetener, approximately as sweet as sucrose, well adapted as a diluent for different oral dosage forms, wet granulation, and hard coating.

8 Description

Maltitol occurs as a white, odorless, sweet, crystalline powder. It is a disaccharide consisting of one glucose unit linked with one sorbitol unit via an α-(1→4) bond.

SEM: 1
Excipient: *Maltisorb P200*
Manufacturer: Roquette Frères



9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for maltitol.

Test	PhEur 2005
Identification	+
Characters	+
Appearance of solution	+
Conductivity	$\leqslant 20\,\mu S{\cdot}cm^{-1}$
Reducing sugars	$\leqslant 0.2\%$
Related substances	+
Lead	$\leqslant 0.5$ ppm
Nickel	$\leqslant 1$ ppm
Water	$\leqslant 1.0\%$
Microbial contamination	
Aerobic bacteria	$\leqslant 10^2/g$
Fungi	$\leqslant 10^2/g$
Bacterial endotoxins	+
Assay (dried basis)	98.0–102.0%

10 Typical Properties

Compressibility: 9.5%
Density (bulk): 0.79 g/cm^3 (1)
Density (tapped): 0.95 g/cm^3 (1)
Flowability: 5 seconds(1)
Melting point: 148–151°C

Particle size distribution: 95% ⩽ 500 μm, 40% ⩾ 100 μm in size for *Maltisorb P200* (Roquette); 95% ⩽ 200 μm, 50% ⩾ 100 μm in size for *Maltisorb P90* (Roquette).
Solubility: freely soluble in water. *See also* Table II.
Viscosity (dynamic): *see* Table III.

Table II: Solubility of maltitol (*Maltisorb*).(1)

Solvent	Solubility at 20°C unless otherwise stated
Water	1 in 0.67 1 in 0.48 at 40°C 1 in 0.33 at 60°C 1 in 0.22 at 80°C 1 in 0.18 at 90°C

Table III: Viscosity (dynamic) of aqueous maltitol (*Maltisorb*) solutions at 20°C.(1)

Concentration of aqueous maltitol solution (% w/v)	Viscosity (mPa s)
10	8
20	10
30	11
40	15
50	24
60	70

11 Stability and Storage Conditions

Maltitol has good thermal and chemical stability. When it is heated at temperatures above 200°C, decomposition begins (depending on time, temperature, and other prevailing conditions). Maltitol does not undergo browning reactions with amino acids, and absorbs atmospheric moisture only at relative humidities of 89% and above, at 20°C.

12 Incompatibilities

—

13 Method of Manufacture

Maltitol is obtained from hydrogenated maltose syrup. Starch is hydrolyzed to yield a high-concentration maltose syrup, which is hydrogenated with a catalyst. After purification and concentration, the syrup is crystallized.

14 Safety

Maltitol is used in oral pharmaceutical formulations, confectionery, and food products and is considered to be noncariogenic. It is generally regarded as a nontoxic, nonallergenic, and nonirritant material.

Digestion of maltitol follows two different metabolic pathways: absorption in the small intestine and fermentation in the large intestine (colon). These two metabolic pathways must thus be considered when evaluating the energy value.

The hydrolysis of maltitol in the small intestine releases sorbitol and glucose. Glucose is actively transported and rapidly absorbed, whereas sorbitol absorption is passive. The nonabsorbed sorbitol and nonhydrolyzed maltitol are fermented by the microflora in the colon. The relative importance of the two absorption pathways depends on numerous individual factors and is related to the quantity of maltitol ingested. Excessive oral consumption (>50 g daily) may cause flatulence and diarrhea.

Maltitol exhibits a low glycemic index and can therefore, under medical supervision, have a place in the diet of diabetic patients. The intake of maltitol must be taken into account for the calculation of the daily glucidic allowance.

The WHO in considering the safety of maltitol did not set a value for the acceptable daily intake since the levels used in food to achieve a desired effect were not considered a hazard to health.(2,3)

15 Handling Precautions

Observe normal precautions appropriate to circumstances and quantity of material handled. Eye protection and gloves are recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in oral pharmaceutical formulations. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Sorbitol.

18 Comments

Maltitol is not fermented by oral bacteria and is neither acidogenic nor cariogenic. A specification for maltitol syrup is contained in the Food Chemicals Codex (FCC). The EINECS number for maltitol is 209-567-0.

19 Specific References

1 Roquette Frères. Technical literature: *Maltisorb* crystalline maltitol, 1999.
2 FAO/WHO. Evaluation of certain food additives and contaminants. Thirty-third report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1989; No. 776.
3 FAO/WHO. Evaluation of certain food additives and contaminants. Forty-sixth report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1997; No. 868.

20 General References

Moskowitz AH. Maltitol and hydrogenated starch hydrolysate. In: Nabors LO, Gelardi RC, eds. *Alternative Sweeteners*, 2nd edn. New York: Marcel Dekker, 1991: 259–282.
Portman MO, Kilcast D. Psycho-physical characterization of new sweeteners of commercial importance for the EC food industry. *Food Chem* 1996; **56**(3): 291–302.

21 Authors

X Duriez.

22 Date of Revision

26 August 2005.

Maltitol Solution

1 Nonproprietary Names

BP: Liquid maltitol
PhEur: Maltitolum liquidum
USPNF: Maltitol solution

2 Synonyms

E965; hydrogenated glucose syrup; *Finmalt L*; *Lycasin HBC*; *Lycasin 80/55*; *Maltisorb 75/75*; *Maltisweet 3145*; maltitol syrup.

3 Chemical Name and CAS Registry Number

Maltitol solution [9053-46-7]

4 Empirical Formula and Molecular Weight

The PhEur 2005 describes liquid maltitol as an aqueous solution of a hydrogenated, partly hydrolyzed starch, with not less than 68% w/w of solid matter and not more than 85% w/w. This is composed of a mixture of mainly D-maltitol ($\geqslant$50% w/w), D-sorbitol ($\leqslant$8% w/w), and hydrogenated oligo- and polysaccharides, all quoted on an anhydrous basis.

The USPNF 23 describes maltitol solution as an aqueous solution of a hydrogenated, partially hydrolyzed starch. It contains, on the anhydrous basis, not less than 50% w/w of D-maltitol ($C_{12}H_{24}O_{11}$) and not more than 8.0% w/w of D-sorbitol ($C_6H_{14}O_6$). *See also* Section 18.

5 Structural Formula

See Section 4.

6 Functional Category

Suspending agent; sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

Maltitol solution is used in oral pharmaceutical formulations as a bulk sweetening agent, either alone or in combination with other excipients, such as sorbitol. Maltitol solution is also used as a suspending agent in oral suspensions as an alternative to sucrose syrup since it is viscous, noncariogenic, and has a low calorific value. It is also noncrystallizing and therefore prevents 'cap-locking' in syrups and elixirs.

Maltitol solution is additionally used in the preparation of pharmaceutical lozenges(1) and is also used in confectionery and food products.

8 Description

Maltitol solution is a colorless and odorless, clear viscous liquid. It is sweet-tasting (approximately 75% the sweetness of sucrose).

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for maltitol solution.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Conductivity	$\leqslant 10\,\mu S{\cdot}cm^{-1}$	—
pH	—	5.0–7.5
Reducing sugars	$\leqslant$0.2%	$\leqslant$0.3%
Lead	$\leqslant$0.5 ppm	—
Nickel	$\leqslant$1 ppm	$\leqslant$1 ppm
Water	15.0–32.0%	$\leqslant$31.5%
Residue on ignition	—	$\leqslant$0.1%
Maltitol (dried basis)	$\geqslant$50.0%	$\geqslant$50.0%
Sorbitol (dried basis)	$\leqslant$8.0%	$\leqslant$8.0%

10 Typical Properties

Boiling point: 105°C
Flash point: >150°C
Density: 1.36 g/cm^3 at 20°C
Heat of combustion: 10.0 kJ/g (2.4 kcal/g)
Osmolarity: the osmolarity of an aqueous maltitol solution is similar to that of a sucrose solution of the same concentration. A 10% v/v aqueous solution of *Lycasin 80/55* (Roquette) is iso-osmotic with serum.
Refractive index: n_D^{20} = 1.478
Solubility: miscible with ethanol (provided the ethanol concentration is less than 55%), glycerin, propylene glycol, and water. Insoluble in mineral and vegetable oils.
Viscosity (dynamic): maltitol solution is a viscous, syrupy, liquid. At 20°C, a solution of *Lycasin 80/55* (Roquette) containing 75% of dry substances has a viscosity of approximately 2000 mPa s (2000 cP). With increasing temperature, the viscosity of a maltitol solution is reduced; *see* Figure 1. The viscosity of maltitol solutions also decreases with decreasing concentration of dry solids, at a constant temperature. Maltitol solution may also be mixed with sorbitol solution to obtain blends of a desired viscosity.

11 Stability and Storage Conditions

Maltitol solution is stable for at least 2 years at room temperature and pH 3–9. Following storage for 3 months at 50°C, maltitol solution at pH 2 underwent slight hydrolysis (1.2%) and became yellow colored. At pH 3, and the same storage conditions, no color change was apparent although very slight hydrolysis occurred (0.2%). At pH 4–9, no hydrolysis occurred although a very slight yellow color was formed under alkaline conditions.(2)

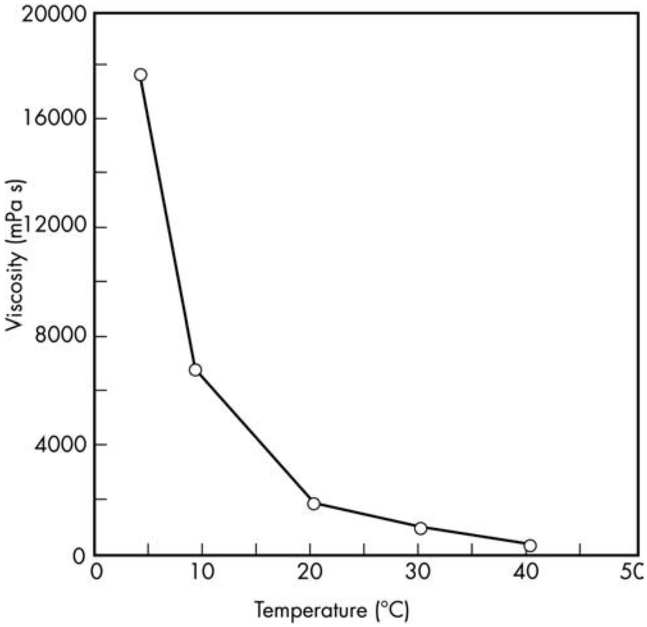


Figure 1: Viscosity of maltitol solution (*Lycasin 80/55*), containing 75% of dry substances, at different temperatures.

Formulations containing maltitol solution should be preserved with an antimicrobial preservative such as sodium benzoate or a mixture of parabens. Maltitol solution is noncrystallizing.

Maltitol solution should be stored in a well-closed container, in a cool, dry place.

12 Incompatibilities

—

13 Method of Manufacture

Maltitol solution is prepared by the hydrogenation of a high-maltose syrup that is obtained from starch by enzymatic hydrolysis. The maltitol solution produced from this process consists of the hydrogenated homologs of the oligosaccharides contained in the original syrup.

14 Safety

Maltitol solution is used in oral pharmaceutical formulations, confectionery, and food products and is considered to be less cariogenic than sucrose.(3–6) It is generally regarded as a nontoxic, nonallergenic, and nonirritant material. However, excessive oral consumption (more than 50 g daily) may cause flatulence and diarrhea.

The WHO, in considering the safety of maltitol solution, did not set a value for the acceptable daily intake since the levels used in food to achieve a desired effect were not considered a hazard to health.(7,8)

LD_{50} (rat, IP): 20 g/kg(9)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Accepted for use in confectionery, foods, and nonparenteral pharmaceutical formulations in Europe and the USA. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Maltitol; sorbitol.

18 Comments

Hydrogenated glucose syrup is a generic term used to describe aqueous mixtures containing mainly D-maltitol, along with D-sorbitol and hydrogenated oligosaccharides and polysaccharides. Such mixtures can vary widely in their composition and hence physical and chemical properties. Products containing up to 90% of maltitol are usually known as maltitol syrup or maltitol solution. Preparations containing a minimum of 98% of maltitol are designated maltitol.

19 Specific References

1 Grenby TH. Dental properties of antiseptic throat lozenges formulated with sugars or Lycasin. *J Clin Pharm Ther* 1995; **20**: 235–241.
2 Roquette. Technical literature: *Lycasin the sweetener for sugarless pharmaceuticals*. 1993.
3 Frostell G, Birkhed D. Acid production from Swedish Lycasin (candy quality) and French Lycasin (80/55) in human dental plaques. *Caries Res* 1978; **12**: 256–263.
4 Grenby TH. Dental and nutritional effects of Lycasins replacing sucrose in the diet of laboratory rats. *J Dent Res* 1982; **61**: 557.
5 Würsch P, Koellreutter B. Maltitol and maltotriitol as inhibitors of acid production in human dental plaque. *Caries Res* 1982; **16**: 90–95.
6 Havenaar R, Drost JS, de Stoppelaar JD, *et al*. Potential cariogenicity of Lycasin 80/55 in comparison to starch, sucrose, xylitol, sorbitol and L-sorbose in rats. *Caries Res* 1984; **18**: 375–384.
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X Duriez.

22 Date of Revision

26 August 2005.

Maltodextrin

1 Nonproprietary Names

BP: Maltodextrin
PhEur: Maltodextrinum
USPNF: Maltodextrin

2 Synonyms

*C*Dry MD*; *C*PharmDry*; *Glucidex*; *Glucodry*; *Lycatab DSH*; *Maldex*; *Malta*Gran*; *Maltrin*; *Maltrin QD*; *Paselli MD10 PH*; *Rice*Trin*; *Star-Dri*; *Tapi.*

3 Chemical Name and CAS Registry Number

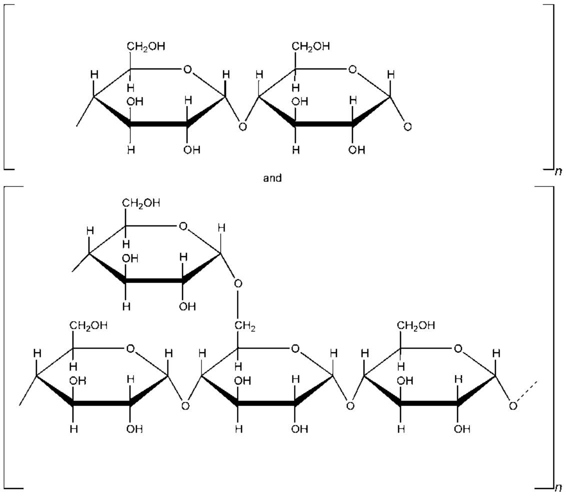
Maltodextrin [9050-36-6]

4 Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n \cdot H_2O$ 900–9000

The USPNF 23 describes maltodextrin as a nonsweet, nutritive saccharide mixture of polymers that consist of D-glucose units, with a dextrose equivalent (DE) less than 20; *see also* Section 18. The D-glucose units are linked primarily by α-(1→4) bonds but there are branched segments linked by α-(1→6) bonds. It is prepared by the partial hydrolysis of a food-grade starch with suitable acids and/or enzymes.

5 Structural Formula



6 Functional Category

Coating agent; tablet and capsule diluent; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Maltodextrin is used in tablet formulations as a binder and diluent in both direct-compression and wet-granulation or agglomeration processes.$^{(1-7)}$ Maltodextrin appears to have no adverse effect on the rate of dissolution of tablet and capsule formulations; magnesium stearate 0.5–1.0% may be used as a lubricant. It has been used as a carrier in a spray-dried redispersible oil-in-water emulsion to improve the bioavailability of poorly soluble drugs.$^{(8)}$ Maltodextrin may also be used as a tablet film former in aqueous film-coating processes. Maltodextrin grades with a high DE value are particularly useful in chewable tablet formulations.

Maltodextrin may also be used in pharmaceutical formulations to increase the viscosity of solutions and to prevent the crystallization of syrups. Therapeutically, maltodextrin is often used as a carbohydrate source in oral nutritional supplements because solutions with a lower osmolarity than isocaloric dextrose solutions can be prepared. At body osmolarity, maltodextrin solutions provide a higher caloric density than sugars.

Maltodextrin is also widely used in confectionery and food products, as well as personal care applications. *See* Table I.

Table I: Uses of maltodextrin.

Use	Concentration (%)
Aqueous film-coating	2–10
Carrier	10–99
Crystallization inhibitor for lozenges and syrups	5–20
Osmolarity regulator for solutions	10–50
Spray-drying aid	20–80
Tablet binder (direct compression)	2–40
Tablet binder (wet granulation)	3–10

8 Description

Maltodextrin occurs as a nonsweet, odorless, white powder or granules. The solubility, hygroscopicity, sweetness, and compressibility of maltodextrin increase as the DE increases. The USPNF 23 states that it may be physically modified to improve its physical and functional characteristics.

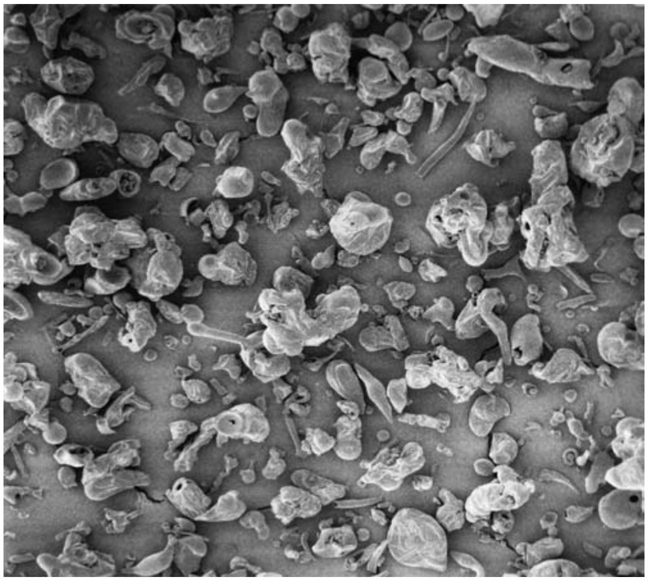
9 Pharmacopeial Specifications

See Table II.

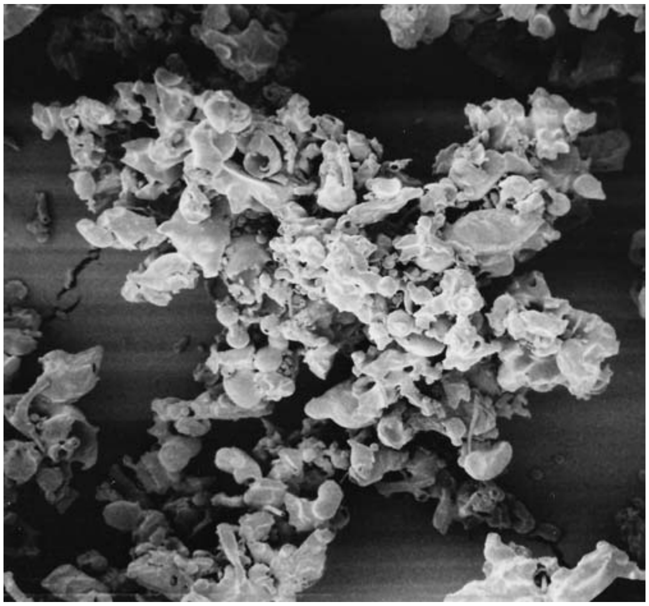
Table II: Pharmacopeial specifications for maltodextrin.

Test	PhEur 2005	USPNF 23
Identification	+	—
Characters	+	—
Microbial limits	+	+
pH (20% w/v solution)	4.0–7.0	4.0–7.0
Loss on drying	≤6.0%	≤6.0%
Residue on ignition	≤0.5%	≤0.5%
Heavy metals	≤10 ppm	≤5 ppm
Protein	—	≤0.1%
Sulfur dioxide	≤20 ppm	≤40 ppm
Dextrose equivalent	+	≤20

SEM: 1
Excipient: Maltodextrin (Maltrin M100)
Manufacturer: Grain Processing Corp.
Magnification: 100×



SEM: 2
Excipient: Maltodextrin (Maltrin QD M500)
Manufacturer: Grain Processing Corp.
Magnification: 100×



10 Typical Properties

Angle of repose:
35.2° for *Maltrin QD M500*;(5)
28.4° for *Maltrin M510*.(5)

Density (bulk):
0.43 g/cm^3 for *Lycatab DSH*;
0.26 g/cm^3 for *Maltrin QD M500*;
0.51 g/cm^3 for *Maltrin M040*;
0.54 g/cm^3 for *Maltrin M050*;
0.54 g/cm^3 for *Maltrin M100*;
0.57 g/cm^3 for *Maltrin M150*;
0.61 g/cm^3 for *Maltrin M180*;
0.30 g/cm^3 for *Maltrin QD M440*;
0.56 g/cm^3 for *Maltrin M510*;
0.37 g/cm^3 for *Maltrin QD M550*;
0.40 g/cm^3 for *Maltrin QD M580*;
0.13 g/cm^3 for *Maltrin M700*.

Density (tapped):
0.63 g/cm^3 for *Lycatab DSH*;
0.32 g/cm^3 for *Maltrin QD M500*;
0.54 g/cm^3 for *Maltrin M510*.(5)

Density (true):
1.419 g/cm^3;
1.334 g/cm^3 for Maltodextrin FCC;
1.410 g/cm^3 for *Maltrin M500*;
1.425 g/cm^3 for *Maltrin M510*.

Moisture content: hygroscopicity increases as DE increases. Maltodextrin is slightly hygroscopic at relative humidities less than 50%. At relative humidities greater than 50%, the hygroscopicity of maltodextrin increases nonlinearly.

Particle size distribution: *Maltrin* is available in various grades with different particle size distributions.

For *Lycatab DSH*: maximum of 15% greater than 200 μm, and minimum of 80% greater than 50 μm in size.

Solubility: freely soluble in water; slightly soluble in ethanol (95%). Solubility increases as DE increases.

Specific surface area:
0.54 m^2/g for *Maltrin QD M500*;
0.31 m^2/g for *Maltrin M510*.(5)

Viscosity (dynamic): less than 20 mPa s (20 cP) for a 20% w/v aqueous solution of *Lycatab DSH*. The viscosity of maltodextrin solutions decreases as the DE increases.

Viscosity is 3.45 mPa s for a 20% w/v aqueous dispersion of *Star-Dri* (Tate & Lyle).

11 Stability and Storage Conditions

Maltodextrin is stable for at least 1 year when stored at a cool temperature (<30°C) and less than 50% relative humidity. Maltodextrin solutions may require the addition of an antimicrobial preservative.

Maltodextrin should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Under certain pH and temperature conditions maltodextrin may undergo Maillard reactions with amino acids to produce yellowing or browning. Incompatible with strong oxidizing agents.

13 Method of Manufacture

Maltodextrin is prepared by heating and treating starch with acid and/or enzymes in the presence of water. This process partially hydrolyzes the starch, to produce a solution of glucose polymers of varying chain length. This solution is then filtered, concentrated, and dried to obtain maltodextrin.

14 Safety

Maltodextrin is a readily digestible carbohydrate with a nutritional value of approximately 17 kJ/g (4 kcal/g). In the USA, it is generally recognized as safe (GRAS) as a direct human food ingredient at levels consistent with current good manufacturing practices. As an excipient, maltodextrin is generally regarded as a nonirritant and nontoxic material.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended. Maltodextrin should be handled in a well-ventilated environment and excessive dust generation should be avoided.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral tablets and granules). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Corn syrup solids; dextrates; dextrin; starch.

Corn syrup solids

Comments: corn syrup solids are glucose polymers with a DE $\geqslant 20$ and are prepared, in a similar manner to maltodextrin, by the partial hydrolysis of starch.

18 Comments

Various different grades of maltodextrin are commercially available for food and pharmaceutical applications from a number of suppliers: e.g. *Lycatab DS* (Roquette Frères), *Maltrin* (Grain Processing Corp.) and *Star-Dri* (Tate & Lyle). The grades have different physical properties such as solubility and viscosity, depending upon their DE value. The dextrose equivalent (DE) value is a measure of the extent of starch-polymer hydrolysis and is defined as the reducing power of a substance expressed in grams of D-glucose per 100 g of the dry substance.

A specification for maltodextrin is contained in the Food Chemicals Codex (FCC). The EINECS number for maltodextrin is 232-940-4.

19 Specific References

1 Li LC, Peck GE. The effect of moisture content on the compression properties of maltodextrins. *J Pharm Pharmacol* 1990; **42**(4): 272–275.
2 Li LC, Peck GE. The effect of agglomeration methods on the micrometric properties of a maltodextrin product *Maltrin 150*. *Drug Dev Ind Pharm* 1990; **16**: 1491–1503.
3 Papadimitriou E, Efentakis M, Choulis NH. Evaluation of maltodextrins as excipients for direct compression tablets and their influence on the rate of dissolution. *Int J Pharm* 1992; **86**: 131–136.
4 Visavarungroj N, Remon JP. Evaluation of maltodextrin as binding agent. *Drug Dev Ind Pharm* 1992; **18**: 1691–1700.
5 Mollan MJ, Çelik M. Characterization of directly compressible maltodextrins manufactured by three different processes. *Drug Dev Ind Pharm* 1993; **19**: 2335–2358.
6 Muñoz-Ruiz A, Monedero Perales MC, Velasco Antequera MV, Jiménez-Castellanos MR. Physical and rheological properties of raw materials. *STP Pharma (Sci)* 1993; **3**: 307–312.
7 Symecko CW, Romero AJ, Rhodes CT. Comparative evaluation of two pharmaceutical binders in the wet granulation of hydrochlorothiazide: Lycatb DSH vs. Kollidon 30. *Drug Dev Ind Pharm* 1993; **19**: 1131–1141.
8 Dollo G, Le Carre P, Guerin A, *et al*. Spray-dried redispersible oil-in-water emulsion to improve oral bioavailability of poorly soluble drugs. *Eur J Pharm Sci* 2003; **19**(4): 273–280.

20 General References

Grain Processing Corporation. Technical literature: *Maltrin maltodextrins and corn syrup solids for pharmaceuticals*, 1998.
Primera Foods. Maltodextrins. http://www.primerafoods.com/mss.asp (accessed 24 August 2005).
Roquette Frères. Technical literature: *Lycatab DSH excipient for wet granulation*, 1992.
Shah A, Buckton G, Booth S. Characterisation of maltodextrins using isothermal microcalorimetry. *J Pharm Pharmacol* 2000; **52** (Suppl.): 183.

21 Authors

SO Freers.

22 Date of Revision

24 August 2005.

Maltol

1 Nonproprietary Names

None adopted.

2 Synonyms

3-Hydroxy-2-methyl-(1,4-pyran); 3-hydroxy-2-methyl-4-pyrone; larixinic acid; 2-methyl-3-hydroxy-4-pyrone; 2-methyl pyromeconic acid; *Palatone*; *Veltol*.

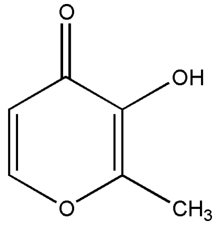
3 Chemical Name and CAS Registry Number

3-Hydroxy-2-methyl-4*H*-pyran-4-one [118-71-8]

4 Empirical Formula and Molecular Weight

$C_6H_6O_3$ 126.11

5 Structural Formula



6 Functional Category

Flavor enhancer; flavoring agent.

7 Applications in Pharmaceutical Formulation or Technology

Maltol is used in pharmaceutical formulations and food products as a flavoring agent or flavor enhancer. In foods, it is used at concentrations up to 30 ppm, particularly with fruit flavorings, although it is also used to impart a freshly baked odor and flavor to bread and cakes. When used at concentrations of 5–75 ppm, maltol potentiates the sweetness of a food product, permitting a reduction in sugar content of up to 15% while maintaining the same level of sweetness. Maltol is also used at low levels in perfumery.

8 Description

White crystalline solid with a characteristic, caramel-like odor and taste. In dilute solution it possesses a sweet, strawberry-like or pineapple-like flavor and odor.

9 Pharmacopeial Specifications

See Section 18.

10 Typical Properties

Acidity/alkalinity: pH = 5.3 (0.5% w/v aqueous solution)
Melting point: 162–164°C (begins to sublime at 93°C)
Solubility: *see* Table I.

Table I: Solubility of maltol.

Solvent	Solubility at 20°C
Chloroform	Freely soluble
Diethyl ether	Sparingly soluble
Ethanol (95%)	1 in 21
Glycerin	1 in 80
Propan-2-ol	1 in 53
Propylene glycol	1 in 28
Water	1 in 83

11 Stability and Storage Conditions

Maltol solutions may be stored in glass or plastic containers. The bulk material should be stored in a well-closed container, protected from light, in a cool, dry place. *See also* Section 12.

12 Incompatibilities

Concentrated solutions in metal containers, including some grades of stainless steel, may discolor on storage.

13 Method of Manufacture

Maltol is mainly isolated from naturally occurring sources such as beechwood and other wood tars; pine needles; chicory; and the bark of young larch trees. It may also be synthesized by the alkaline hydrolysis of streptomycin salts or by a number of other synthetic methods.

14 Safety

Maltol is generally regarded as an essentially nontoxic and nonirritant material. In animal feeding studies, it has been shown to be well tolerated with no adverse toxic, reproductive, or embryogenic effects observed in rats and dogs fed daily intakes of up to 200 mg/kg of maltol, for 2 years.(1) The WHO has set an acceptable daily intake for maltol at up to 1 mg/kg body-weight.(2) A case of allergic contact dermatitis, attributed to the use of maltol in a lip ointment, has been reported.(3)

LD_{50} (chicken, oral): 3.72 g/kg(4)
LD_{50} (guinea pig, oral): 1.41 g/kg
LD_{50} (mouse, oral): 0.85 g/kg
LD_{50} (mouse, SC): 0.82 g/kg
LD_{50} (rabbit, oral): 1.62 g/kg
LD_{50} (rat, oral): 1.41 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Maltol should be used in a well-ventilated environment. Eye protection is recommended.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral solutions and syrups). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Ethyl maltol.

18 Comments

Maltol is a good chelating agent and various metal complexes, e.g., aluminum maltol and ferric maltol have been investigated as potentially useful therapeutic or experimental agents.(5–8)

Maltol is a constituent of Korean red ginseng.(9)

Although not included in any pharmacopeias, a specification for maltol is contained in the Food Chemicals Codex (FCC), *see* Table II.(10)

Table II: Food Chemicals Codex specifications for maltol.

Test	FCC 1996
Identification	+
Heavy metals (as lead)	⩽0.002%
Lead	⩽10 ppm
Melting range	160–164°C
Residue on ignition	⩽0.2%
Water	⩽0.5%
Assay	⩾99.0%

19 Specific References

1 Gralla EJ, Stebbins RB, Coleman GL, Delahunt CS. Toxicity studies with ethyl maltol. *Toxicol Appl Pharmacol* 1969; **15**: 604–613.
2 FAO/WHO. Evaluation of certain food additives. Twenty-fifth report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1981; No. 669.
3 Taylor AE, Lever L, Lawrence CM. Allergic contact dermatitis from strawberry lipsalve. *Contact Dermatitis* 1996; **34**(2): 142–143.
4 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials,* 11th edn. New York: Wiley, 2004: 2275.
5 Finnegan MM, Rettig SJ, Orvig C. A neutral water-soluble aluminum complex of neurological interest. *J Am Chem Soc* 1986; **108**: 5033–5035.
6 Barrand MA, Callingham BA, Hider RC. Effects of the pyrones, maltol and ethyl maltol, on iron absorption from the rat small intestine. *J Pharm Pharmacol* 1987; **39**: 203–211.
7 Singh RK, Barrand MA. Lipid peroxidation effects of a novel iron compound, ferric maltol. A comparison with ferrous sulfate. *J Pharm Pharmacol* 1990; **42**: 276–279.
8 Kelsey SM, Hider RC, Bloor JR, *et al.* Absorption of low and therapeutic doses of ferric maltol, a novel ferric iron compound, in iron deficient subjects using a single dose iron absorption test. *J Clin Pharm Ther* 1991; **16**: 117–122.
9 Wei J. Studies on the constituents of Korean red ginseng – the isolation and identification of 3-hydroxy-2-methyl-4-pyrone [in Chinese]. *Acta Pharmaceutica Sinica* 1982; **17**: 549–550.
10 *Food Chemicals Codex,* 4th edn. Washington, DC: National Academy Press, 1996: 240–241.

20 General References

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21 Authors

PJ Weller.

22 Date of Revision

11 August 2005.

Maltose

1 Nonproprietary Names

JP: Maltose
USPNF: Maltose

2 Synonyms

Advantose 100; *Finetose*; *Finetose F*; 4-O-α-D-glucopyranosyl-β-D-glucose; 4-(α-D-glucosido)-D-glucose; malt sugar; maltobiose; *Maltodiose*; *Maltose HH*; *Maltose HHH*; *Sunmalt*; *Sunmalt S*.

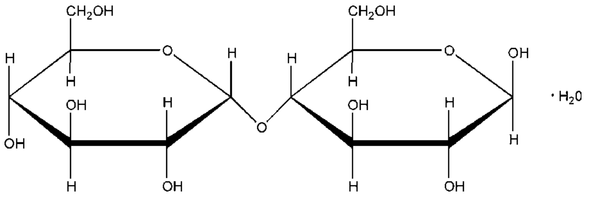
3 Chemical Name and CAS Registry Number

4-O-α-D-Glucopyranosyl-β-D-glucopyranose anhydrous [69-79-4]
4-O-α-D-Glucopyranosyl-β-D-glucopyranose monohydrate [6363-53-7]

4 Empirical Formula and Molecular Weight

$C_{12}H_{22}O_{11}$	342.31 (anhydrous)
$C_{12}H_{22}O_{11}{\cdot}H_2O$	360.31 (monohydrate)

5 Structural Formula



6 Functional Category

Sweetening agent; tablet diluent.

7 Applications in Pharmaceutical Formulation or Technology

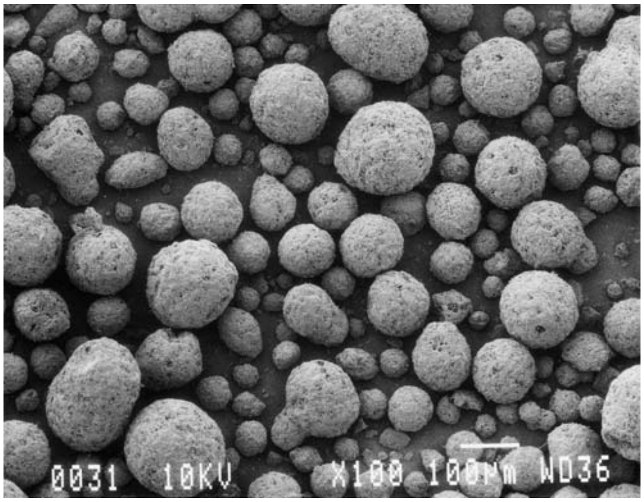
Maltose is a disaccharide carbohydrate widely used in foods and pharmaceuticals. In parenteral products, maltose may be used as a source of sugar, particularly for diabetic patients.

Crystalline maltose is used as a direct-compression tablet excipient in chewable and nonchewable tablets.$^{(1–3)}$

8 Description

Maltose occurs as white crystals or as a crystalline powder. It is odorless and has a sweet taste approximately 30% that of sucrose.

SEM: 1
Excipient: Crystalline maltose
Manufacturer: SPI Pharma Group
Lot No.: 8K110947
Magnification: 100×



9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for maltose.

Test	JP 2001	USPNF 23
Identification	+	+
Specific rotation	+126° to +131°	—
pH	4.5–6.5	—
for anhydrous	—	3.7–4.4
for monohydrate	—	4.0–5.5
Clarity and color of solution	+	—
Chloride	<0.018%	—
Sulfate	<0.024%	—
Heavy metals	<4 ppm	⩽5 ppm
Arsenic	<1.3 ppm	—
Dextrin, soluble starch and sulfite	+	+
Nitrogen	<0.01%	—
Related substances	+	—
Loss on drying	<0.5%	—
Water	—	—
for anhydrous	—	⩽1.5%
for monohydrate	—	5.0–6.5%
Residue on ignition	<0.10%	⩽0.05%
Assay (dried basis)	>98.0%	>92.0%

10 Typical Properties

Acidity/alkalinity: pH = 4.5–6.5 for a 10% w/v aqueous solution.

Angle of repose: 37.1° for *Advantose 100*.(3)
Density (bulk): 0.67–0.72 g/cm^3 for *Advantose 100*.(1)
Density (tapped): 0.73–0.81 g/cm^3 for *Advantose 100*.(1)
Dissociation constant: $pK_a = 12.05$ at 21°C
Flash point: >149°C for *Advantose 100*.(1)
Flowability: 18% (Carr compressibility index) for *Advantose 100*.(3)
Melting point: 120–125°C.(4)
Particle size distribution: 15–20% greater than 300 μm, and 70–75% greater than 150 μm in size for *Advantose 100*.(1)
Specific surface area: 0.08 m^2/g for *Advantose 100*.(1)
Solubility: very soluble in water; very slightly soluble in cold ethanol (95%); practically insoluble in ether.

11 Stability and Storage Conditions

Maltose should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Maltose may react with oxidizing agents.

13 Method of Manufacture

Maltose monohydrate is prepared by the enzymatic degradation of starch.

14 Safety

Maltose is used in oral and parenteral pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material. However, there has been a single report of a liver transplantation patient with renal failure who developed hyponatremia following intravenous infusion of normal immunoglobulin in 10% maltose. The effect, which recurred on each of four successive infusions, resembled that of hyperglycemia and was thought to be due to accumulation of maltose and other osmotically active metabolites in the extracellular fluid.(4)

LD_{50} (mouse, IV): 26.8 g/kg(5)
LD_{50} (mouse, SC): 38.6 g/kg
LD_{50} (rabbit, IV): 25.2 g/kg
LD_{50} (rat, IP): 30.6 g/kg
LD_{50} (rat, IV): 15.3 g/kg
LD_{50} (rat, oral): 34.8 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, rubber or plastic gloves, and a dust respirator are recommended. When heated to decomposition, maltose emits acrid smoke and irritating fumes.

16 Regulatory Status

In the USA, maltose is considered as a food by the FDA and is therefore not subject to food additive and GRAS regulations. Included in the FDA Inactive Ingredients Guide (oral solutions). Included in the Canadian List of Acceptable Non-medicinal Ingredients. Included in parenteral products available in a number of countries worldwide.

17 Related Substances

Glucose, liquid.

18 Comments

Crystalline maltose, e.g. *Advantose 100* (SPI Pharma Group), is spray-dried to produce spherical particles with good flow properties. The material is also nonhygroscopic and is highly compressible.

The EINECS number for maltose is 200-716-5.

19 Specific References

1 SPI Pharma Group. Technical literature: *Advantose 100 maltose*, 2004.
2 Bowe KE, Billig JL, Schwartz JB, *et al*. Crystalline maltose: a direct compression pharmaceutical excipient. *Pharm Technol Eur* 1998; **10**(5): 34, 36, 37, 40.
3 Mulderrig KB. Placebo evaluation of selected sugar-based excipients in pharmaceutical and nutraceutical tableting. *Pharm Technol* 2000; **24**(5): 34, 36, 38, 40, 42, 44.
4 Palevsky PM, Rendulic D, Diven WF. Maltose-induced hyponatremia. *Ann Intern Med* 1993; **118**(7): 526–528.
5 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 2275.

20 General References

Japan Pharmaceutical Excipients Council. *Japanese Pharmaceutical Excipients Directory 1996*. Tokyo: Yakuji Nippo, 1996: 299.

21 Authors

H Wang.

22 Date of Revision

11 August 2005.

Mannitol

1 Nonproprietary Names

BP: Mannitol
JP: D-Mannitol
PhEur: Mannitolum
USP: Mannitol

2 Synonyms

Cordycepic acid; *C*PharmMannidex*; E421; manna sugar; D-mannite; mannite; *Mannogem*; *Pearlitol*.

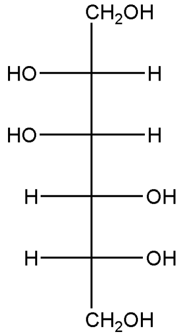
3 Chemical Name and CAS Registry Number

D-Mannitol [69-65-8]

4 Empirical Formula and Molecular Weight

$C_6H_{14}O_6$ 182.17

5 Structural Formula



6 Functional Category

Diluent; diluent for lyphilized preparations; sweetening agent; tablet and capsule diluent; tonicity agent.

7 Applications in Pharmaceutical Formulation or Technology

Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients.(1,2)

Mannitol may be used in direct-compression tablet applications,(3–7) for which the granular and spray-dried forms are available, or in wet granulations.(8) Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouth feel'.(9,10)

In lyophilized preparations, mannitol (20–90% w/w) has been included as a carrier to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plug in a vial.(11–20) A pyrogen-free form is available specifically for this use.

Mannitol has also been used to prevent thickening in aqueous antacid suspensions of aluminum hydroxide (<7% w/v). It has been suggested as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations,(21) and as a carrier in dry powder inhalers.(22,23) It is also used as a diluent in rapidly dispersing oral dosage forms.(24,25) It is used in food applications as a bulking agent.

Therapeutically, mannitol administered parenterally is used as an osmotic diuretic, as a diagnostic agent for kidney function, as an adjunct in the treatment of acute renal failure, and as an agent to reduce intracranial pressure, treat cerebral edema, and reduce intraocular pressure. Given orally, mannitol is not absorbed significantly from the GI tract, but in large doses it can cause osmotic diarrhea; *see* Section 14.

8 Description

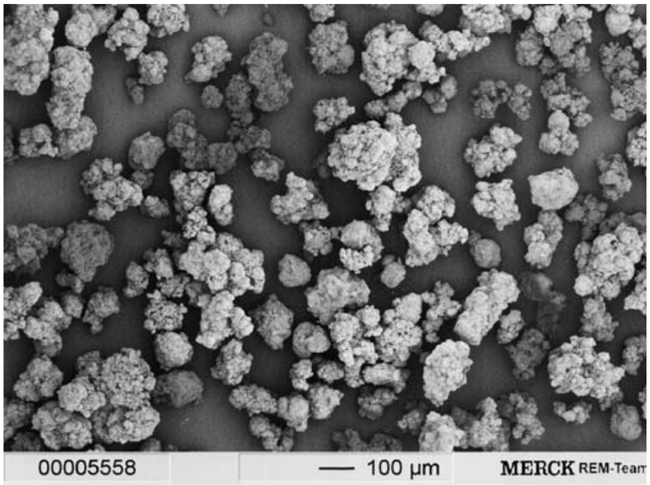
Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol.

Mannitol occurs as a white, odorless, crystalline powder, or free-flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Mannitol shows polymorphism.(26)

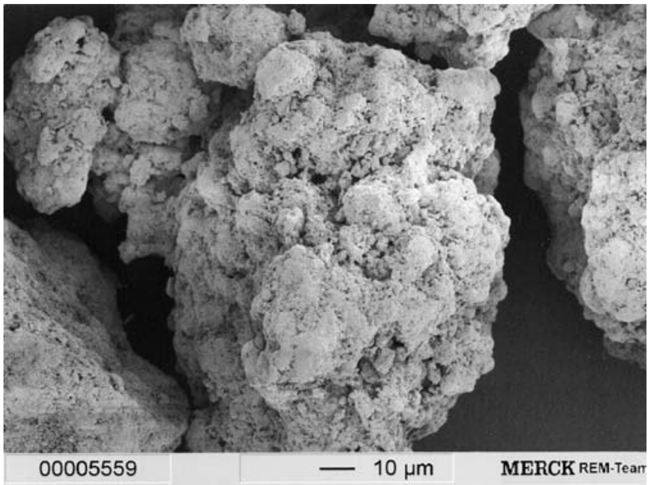
9 Pharmacopeial Specifications

See Table I.

SEM: 1
Excipient: Mannitol
Manufacturer: Merck
Magnification: 50×
Voltage: 3.5 kV



SEM: 2
Excipient: Mannitol
Manufacturer: Merck
Magnification: 500×
Voltage: 3.5 kV



SEM: 3
Excipient: Mannitol powder
Manufacturer: SPI Polyols Inc.
Lot No: 3140G8
Magnification: 100×

10 Typical Properties

Compressibility: *see* Figure 1.
Density (bulk):
0.430 g/cm^3 for powder;
0.7 g/cm^3 for granules.
Density (tapped):
0.734 g/cm^3 for powder;
0.8 g/cm^3 for granules.
Density (true): 1.514 g/cm^3
Dissociation constant: pK_a = 13.5 at 18°C
Flash point: <150°C
Flowability: powder is cohesive, granules are free flowing.
Heat of combustion: 16.57 kJ/g (3.96 kcal/g)
Heat of solution: −120.9 J/g (−28.9 cal/g) at 25°C
Melting point: 166–168°C

SEM: 4
Excipient: Mannitol granular
Manufacturer: SPI Polyols Inc.
Lot No: 2034F8
Magnification: 100×

Moisture content: *see* Figure 2.
Osmolarity: a 5.07% w/v aqueous solution is isoosmotic with serum.
Particle size distribution:
Pearlitol 300 DC: maximum of 0.1% greater than 500 μm and minimum of 90% greater than 200 μm in size;
Pearlitol 400 DC: maximum of 20% greater than 500 μm and minimum of 85% greater than 100 μm in size;
Pearlitol 500 DC: maximum of 0.5% greater than 841 μm and minimum of 90% greater than 150 μm in size.

Average particle diameter is 250 μm for *Pearlitol 300 DC*, 360 μm for *Pearlitol 400 DC* and 520 μm for *Pearlitol 500 DC*.(27) *See also* Figure 3.

Table I: Pharmacopeial specifications for mannitol.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	—	+	—
Solution appearance	+	+	—
Melting range	166–169°C	165–170°C	164–169°C
Specific rotation	+137° to +145°	+23° to +25°	+137° to +145°
Conductivity	–	⩽20 μS·cm^{-1}	—
Acidity	+	—	+
Loss on drying	⩽0.3%	⩽0.5%	⩽0.3%
Chloride	⩽0.007%	—	⩽0.007%
Sulfate	⩽0.01%	—	⩽0.01%
Arsenic	⩽1.3 ppm	—	⩽1 ppm
Lead	–	⩽0.5 ppm	—
Nickel	+	⩽1 ppm	—
Heavy metals	⩽5 ppm	—	—
Reducing sugars	+	⩽0.2%	+
Residue on ignition	⩽0.10%	—	—
Related substances	—	⩽0.1%	—
Bacterial endotoxins	—	⩽4 IU/g[a]	—
Microbial contamination	—	⩽100/g	—
Assay (dried basis)	⩾ 98.0%	98.0–102.0%	96.0–101.5%

[a] Test applied only if the mannitol is to be used in the manufacture of parenteral dosage forms.

Table II: Solubility of mannitol.

Solvent	Solubility at 20°C
Alkalis	Soluble
Ethanol (95%)	1 in 83
Ether	Practically insoluble
Glycerin	1 in 18
Propan-2-ol	1 in 100
Water	1 in 5.5

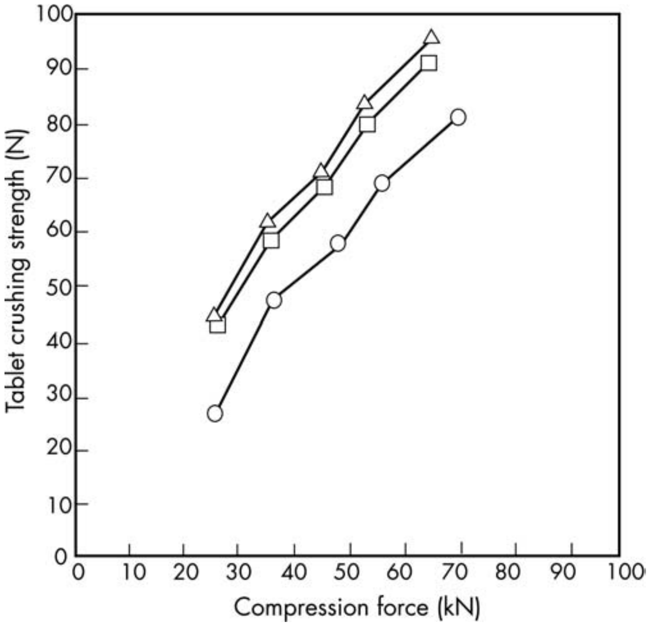


Figure 1: Compression characteristics of granular mannitol (*Pearlitol*, Roquette Frères).
○: *Pearlitol 300DC*
□: *Pearlitol 400DC*
△: *Pearlitol 500DC*
Tablet diameter: 20 mm
Lubricant: magnesium stearate 0.7% w/w for *Pearlitol 400DC* and *Pearlitol 500DC*; magnesium stearate 1% w/w for *Pearlitol 300DC*.

Refractive index: $n_D^{20} = 1.333$
Solubility: *see* Table II.
Specific surface area: 0.37–0.39 m^2/g

11 Stability and Storage Conditions

Mannitol is stable in the dry state and in aqueous solutions. Solutions may be sterilized by filtration or by autoclaving and if necessary may be autoclaved repeatedly with no adverse physical or chemical effects.(28) In solution, mannitol is not attacked by cold, dilute acids or alkalis, nor by atmospheric oxygen in the absence of catalysts. Mannitol does not undergo Maillard reactions.

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride.(29) Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed to contact plastic.(30) Sodium cephapirin at 2 mg/mL and 30 mg/mL concentration is incompatible with 20% w/v aqueous mannitol solution. Mannitol is incompatible with xylitol infusion and may form complexes with some metals such as aluminum, copper, and iron. Reducing sugar impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized formation.(31) Mannitol was found to reduce the oral bioavailability of cimetidine compared to sucrose.(32)

13 Method of Manufacture

Mannitol may be extracted from the dried sap of manna and other natural sources by means of hot alcohol or other selective solvents. It is commercially produced by the catalytic or electrolytic reduction of monosaccharides such as mannose and glucose.

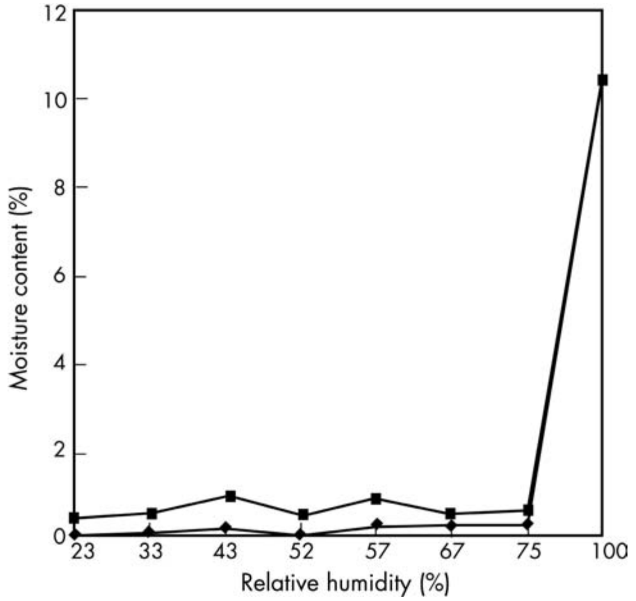


Figure 2: Sorption–desorption isotherm for mannitol.
◆: Sorption equilibrium moisture
■: Desorption equilibrium moisture

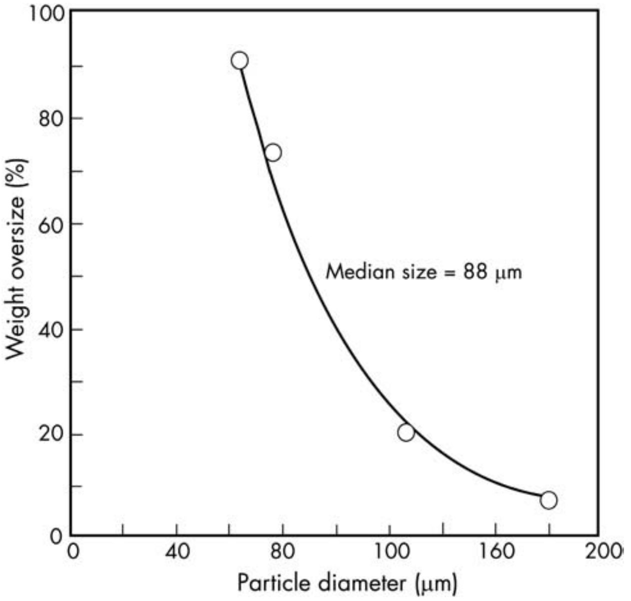


Figure 3: Particle size distribution of mannitol powder.

14 Safety

Mannitol is a naturally occurring sugar alcohol found in animals and plants; it is present in small quantities in almost all vegetables. Laxative effects may occur if mannitol is consumed orally in large quantities.(33) If it is used in foods as a bodying agent and daily ingestion of over 20 g is foreseeable, the product label should bear the statement 'excessive consumption may have a laxative effect'. After intravenous injection, mannitol is not metabolized to any appreciable extent and is minimally reabsorbed by the renal tubule, about 80% of a dose being excreted in the urine in 3 hours.(34)

A number of adverse reactions to mannitol have been reported, primarily following the therapeutic use of 20% w/v aqueous intravenous infusions.(35) The quantity of mannitol used as an excipient is considerably less than that used therapeutically and is consequently associated with a lower incidence of adverse reactions. However, allergic, hypersensitive-type reactions may occur when mannitol is used as an excipient.

An acceptable daily intake of mannitol has not been specified by the WHO since the amount consumed as a sweetening agent was not considered to represent a hazard to health.(36)

LD_{50} (mouse, IP): 14 g/kg(37)
LD_{50} (mouse, IV): 7.47 g/kg
LD_{50} (mouse, oral): 22 g/kg
LD_{50} (rat, IV): 9.69 g/kg
LD_{50} (rat, oral): 13.5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Mannitol may be irritant to the eyes; eye protection is recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IP, IM, IV, and SC injections; infusions; buccal, oral and sublingual tablets, powders and capsules; ophthalmic preparations; topical solutions). Included in nonparenteral and parenteral medicines licensed in the UK.

17 Related Substances

Sorbitol.

18 Comments

Mannitol is an isomer of sorbitol, the difference between the two polyols occurring in the planar orientation of the OH group on the second carbon atom. Each isomer is characterized by its own individual set of properties, the most important difference being the response to moisture. Sorbitol is hygroscopic, while mannitol resists moisture sorption, even at high relative humidities.

Granular mannitol flows well and imparts improved flow properties to other materials. However, it usually cannot be used with concentrations of other materials exceeding 25% by weight. Recommended levels of lubricant are 1% w/w calcium stearate or 1–2% w/w magnesium stearate. Suitable binders for preparing granulations of powdered mannitol are gelatin, methylcellulose 400, starch paste, povidone, and sorbitol. Usually, 3–6 times as much magnesium stearate or 1.5–3 times as much calcium stearate is needed for lubrication of mannitol granulations than is needed for other excipients.

Mannitol has been reported to sublime at 130°C.(38)

A specification for mannitol is contained in the Food Chemicals Codex (FCC). The EINECS number for mannitol is 200-711-8.

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21 Authors

NA Armstrong.

22 Date of Revision

16 August 2005.

Medium-chain Triglycerides

1 Nonproprietary Names

BP: Medium-chain triglycerides
PhEur: Triglycerida saturata media
USPNF: Medium-chain triglycerides

2 Synonyms

Bergabest; caprylic/capric triglyceride; *Captex 300*; *Captex 355*; *Crodamol GTC/C*; glyceryl tricaprylate/caprate; *Labrafac CC*; MCT oil; *Miglyol 810*; *Miglyol 812*; *Myritol*; *Neobee M5*; *Nesatol*; oleum neutrale; oleum vegetable tenue; thin vegetable oil; *Waglinol 3/9280*.

3 Chemical Name and CAS Registry Number

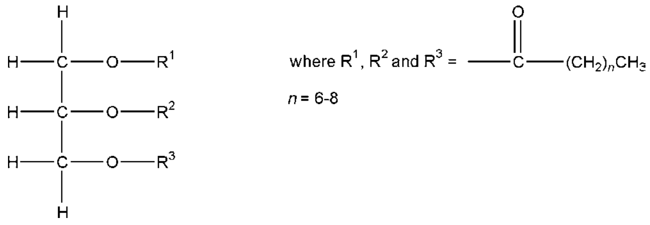
Medium-chain triglycerides [73398-61-5]

4 Empirical Formula and Molecular Weight

≈500 (average)

The PhEur 2005 describes medium-chain triglycerides as the fixed oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera* L. or from the dried endosperm of *Elaeis guineenis* Jacq. They consist of a mixture of triglycerides of saturated fatty acids, mainly of caprylic acid and of capric acid. They contain not less than 95% of saturated fatty acids.

5 Structural Formula



See also Section 4.

6 Functional Category

Emulsifying agent; solvent; suspending agent; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Medium-chain triglycerides have been used in a variety of pharmaceutical formulations including oral, parenteral, and topical preparations.

In oral formulations, medium-chain triglycerides are used as the base for the preparation of oral emulsions, microemulsions, self-emulsifying systems, solutions, or suspensions of drugs that are unstable or insoluble in aqueous media, e.g. calciferol. Medium-chain triglycerides have also been investigated as intestinal-absorption enhancers(1,2) and have additionally been used as a filler in capsules and sugar-coated tablets, and as a lubricant or antiadhesion agent in tablets.

In parenteral formulations, medium-chain triglycerides have similarly been used in the production of emulsions, solutions, or suspensions intended for intravenous administration.(3–9) Medium-chain triglycerides have been particularly investigated for their use in total parenteral nutrition (TPN) regimens in combination with long-chain triglycerides.(4)

In cosmetics and topical pharmaceutical preparations, medium-chain triglycerides are used as a component of ointments, creams, and liquid emulsions.(5) In rectal formulations, medium-chain triglycerides have been used in the preparation of suppositories containing labile materials.

Therapeutically, medium-chain triglycerides have been used as nutritional agents.(10) Diets containing medium-chain triglycerides are used in conditions associated with the malabsorption of fat, such as cystic fibrosis, since medium-chain triglycerides are more readily digested than long-chain triglycerides. Medium-chain triglycerides provide 35 kJ (8.3 kcal) of energy per gram.

Although similar to long-chain triglycerides, medium-chain triglycerides have a number of advantages in pharmaceutical formulations, which include better spreading properties on the skin; no impedance of skin respiration; good penetration properties; good emollient and cosmetic properties; no visible film on the skin surface; good compatibility; good solvent properties; and good stability against oxidation.

8 Description

A colorless to slightly yellowish oily liquid that is practically odorless and tasteless. It solidifies at about 0°C. The oil is free from catalytic residues or the products of cracking.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acid value:
⩽0.1 for *Crodamol GTC/C*;
⩽0.1 for *Miglyol 810*;
⩽0.1 for *Miglyol 812*;
⩽0.05 for *Neobee M5*.

Cloud point:
⩽5°C for *Crodamol GTC/C*;
≈10°C for *Miglyol 810*;
≈10°C for *Miglyol 812*.

Color:
⩽60 (Hazen color index) for *Crodamol GTC/C*;
⩽90 (Hazen color index) for *Miglyol 810*;
⩽60 (Hazen color index) for *Miglyol 812*;
⩽100 (Hazen color index) for *Neobee M5*.

Density:
0.94–0.96 g/cm^3 for *Crodamol GTC/C* at 20°C;
0.94–0.95 g/cm^3 for *Miglyol 810* at 20°C;
0.94–0.95 g/cm^3 for *Miglyol 812* at 20°C;
0.94 g/cm^3 for *Neobee M5* at 20°C.

Table I: Pharmacopeial specifications for medium-chain triglycerides.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	−
Appearance	+	+
Alkaline impurities	+	+
Relative density	0.93–0.96	0.93–0.96
Refractive index	1.440–1.452	1.440–1.452
Viscosity	25–33 mPa s	25–33 mPa s
Acid value	$\leqslant$0.2	$\leqslant$0.2
Hydroxyl value	$\leqslant$10	$\leqslant$10
Iodine value	$\leqslant$1.0	$\leqslant$1.0
Peroxide value	$\leqslant$1.0	$\leqslant$1.0
Saponification value	310–360	310–360
Unsaponifiable matter	$\leqslant$0.5%	$\leqslant$0.5%
Composition of fatty acids		
Caproic acid	$\leqslant$2.0%	$\leqslant$2.0%
Caprylic acid	50.0–80.0%	50.0–80.0%
Capric acid	20.0–50.0%	20.0–50.0%
Lauric acid	$\leqslant$3.0%	$\leqslant$3.0%
Myristic acid	$\leqslant$1.0%	$\leqslant$1.0%
Heavy metals(a)	$\leqslant$10 ppm	$\leqslant$10 ppm
Water	$\leqslant$0.2%	$\leqslant$0.2%
Total ash	$\leqslant$0.1%	$\leqslant$0.1%
Chromium	$\leqslant$0.05 ppm	$\leqslant$0.05 ppm
Copper(a)	$\leqslant$0.1 ppm	$\leqslant$0.1 ppm
Lead(a)	$\leqslant$0.1 ppm	$\leqslant$0.1 ppm
Nickel(a)	$\leqslant$0.2 ppm	$\leqslant$0.1 ppm
Tin(a)	$\leqslant$0.1 ppm	$\leqslant$0.1 ppm

(a) For medium-chain triglycerides intended for use in parenteral nutrition, the test for heavy metals is replaced by the tests for chromium, copper, lead, nickel, and tin.

Freezing point: −5°C for *Neobee M5*
Hydroxyl value: $\leqslant$8 for *Neobee M5*
Iodine number:
  $\leqslant$1.0 for *Crodamol GTC/C*;
  $\leqslant$0.5 for *Miglyol 810*;
  $\leqslant$0.5 for *Miglyol 812*;
  $\leqslant$0.5 for *Neobee M5*.
Moisture content:
  $\leqslant$0.15% w/w for *Crodamol GTC/C*;
  $\leqslant$0.10% w/w for *Miglyol 810*;
  $\leqslant$0.10% w/w for *Miglyol 812*;
  $\leqslant$0.15% w/w for *Neobee M5*.
Peroxide value:
  $\leqslant$1.0 for *Miglyol 810*;
  $\leqslant$1.0 for *Miglyol 812*;
  $\leqslant$0.5 for *Neobee M5*.
Refractive index:
  1.4485–1.4500 for *Crodamol GTC/C* at 20°C;
  1.4485–1.4505 for *Miglyol 810* at 20°C;
  1.4490–1.4510 for *Miglyol 812* at 20°C;
  1.4480–1.4510 for *Neobee M5* at 20°C.
Saponification value:
  325–345 for *Crodamol GTC/C*;
  335–355 for *Miglyol 810*;
  325–345 for *Miglyol 812*;
  335–360 for *Neobee M5*.
Solubility: soluble in all proportions at 20°C in acetone, benzene, 2-butanone, carbon tetrachloride, chloroform, dichloromethane, ethanol, ethanol (95%), ether, ethyl acetate, petroleum ether, special petroleum spirit (boiling range 80–110°C), propan-2-ol, toluene, and xylene. Miscible with long-chain hydrocarbons and triglycerides; practically insoluble in water.
Surface tension:
  32.2 mN/m for *Crodamol GTC/C* at 25°C;
  31.0 mN/m for *Miglyol 810* at 20°C;
  31.1 mN/m for *Miglyol 812* at 20°C;
  32.3 mN/m for *Neobee M5* at 25°C.
Viscosity (dynamic):
  27–30 mPa s (27–30 cP) for *Miglyol 810* at 20°C;
  28–32 mPa s (28–32 cP) for *Miglyol 812* at 20°C;
  23 mPa s (23 cP) for *Neobee M5* at 25°C.

11 Stability and Storage Conditions

Medium-chain triglycerides are stable over the wide range of storage temperatures that can be experienced in tropical and temperate climates. Ideally, however, they should be stored at temperatures not exceeding 25°C and not exposed to temperatures above 40°C for long periods.

In the preparation of microemulsions and self-emulsifying systems, emulsions, or aqueous suspensions of medium-chain triglycerides, care should be taken to avoid microbiological contamination of the preparation, since lipase-producing microorganisms, which become active in the presence of moisture, can cause hydrolysis of the triglycerides. Hydrolysis of the triglycerides is revealed by the characteristic unpleasant odor of free medium-chain fatty acids.

Medium-chain triglycerides may be sterilized by maintaining at 170°C for 1 hour.

At low temperatures, samples of medium-chain triglycerides may become viscous or solidify. Samples should therefore be well melted and mixed before use, although overheating should be avoided.

Medium-chain triglycerides should be stored protected from light in a well-filled and well-closed container. When stored dry, in sealed containers, medium-chain triglycerides remain stable for many years.

12 Incompatibilities

Preparations containing medium-chain triglycerides should not come into contact with polystyrene containers or packaging components since the plastic rapidly becomes brittle upon contact. Low-density polyethylene should also not be used as a packaging material as the medium-chain triglycerides readily penetrate the plastic, especially at high temperatures, forming an oily film on the outside. High-density polyethylene is a suitable packaging material. Closures based on phenol resins should be tested before use for compatibility with medium-chain triglycerides. Polyvinyl chloride packaging should also be tested for compatibility since medium-chain triglycerides can dissolve some plasticisers, such as phthalates, out of the plastic.

Materials recommended as safe for packaging medium-chain triglycerides are low-density polyethylene, polypropylene, glass, and metal.

13 Method of Manufacture

Medium-chain triglycerides are obtained from the fixed oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera* L. Hydrolysis of the fixed oil followed by distillation yields the required fatty acids, which are then re-esterified to produce the medium-chain triglycerides.

Although the PhEur 2005 specifies that medium-chain fatty acids are obtained from coconut oil, medium-chain triglycerides are also to be found in substantial amounts in the kernel oils of certain other types of palm-tree, e.g., palm kernel oil and babassu oil. Some animal products, such as milk-fat, also contain small amounts (up to 4%) of the medium-chain fatty acid esters.

14 Safety

Medium-chain triglycerides are used in a variety of pharmaceutical formulations including oral, parenteral, and topical products and are generally regarded as essentially nontoxic and nonirritant materials.

In acute toxicology studies in animals and humans, no irritant or other adverse reactions have been observed; for example, when they were patch-tested on more than 100 individuals, no irritation was produced on either healthy or eczematous skin. Medium-chain triglycerides are not irritating to the eyes.

Similarly, chronic toxicology studies in animals have shown no harmful adverse effects associated with medium-chain triglycerides following inhalation or intraperitoneal, oral, and parenteral administration.

In humans, administration of 0.5 g/kg body-weight medium-chain triglycerides to healthy individuals produced no change in blood or serum triglycerides compared to subjects receiving the same dose of the long-chain triglyceride triolein.

In patients consuming diets based on medium-chain triglycerides, adverse effects reported include abdominal pain and diarrhea.

LD_{50} (mouse, IV): 3.7 g/kg
LD_{50} (mouse, oral): 29.6 g/kg
LD_{50} (rat, oral): 33.3 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (topical preparations). Included in nonparenteral and parenteral medicines licensed in Europe. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Suppository bases, hard fat; vegetable oil, hydrogenated.

18 Comments

—

19 Specific References

1 Swenson ES, Curatolo WJ. Intestinal permeability enhancement for proteins, peptides and other drugs: mechanisms and potential toxicity. *Adv Drug Del Rev* 1992; **8**: 39–92.
2 Spencer SA, Stammers JP, Hull D. Evaluation of a special low birth weight formula, with and without the use of medium chain triglycerides. *Early Hum Dev* 1986; **13**: 87–95.
3 Bach A, Guisard D, Metais P, Debry G. Metabolic effects following a short and medium-chain triglycerides load in dogs I: infusion of an emulsion of short and medium-chain triglycerides. *Arch Sci Physiol* 1972; **26**: 121–129.
4 Hatton J, Record KE, Bivins BA, *et al.* Safety and efficacy of a lipid emulsion containing medium-chain triglycerides. *Clin Pharm* 1990; **9**: 366–371.
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7 Schaub E, Kern C, Landau R. Pain on injection: a double-blind comparison of propofol with lidocaine pretreatment versus propofol formulated with long- and medium-chain triglycerides. *Anaesth Analg* 2004; **99**: 1699–1702.
8 Cournarie F, Savelli MP, Rosilio V, Bretez F, *et al.* Insulin-loaded w/o/w multiple emulsions: comparison of the performances of systems prepared with medium-chain triglycerides and fish oil. *Eur J Pharm Biopharm* 2004; **58**: 477–482.
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10 Ruppin DC, Middleton WRJ. Clinical use of medium-chain triglycerides. *Drugs* 1980; **20**: 216–224.

20 General References

Akkar A, Namsolleck P, Blaut M, Muller RH. Solubilizing poorly soluble antimycotic agents by emulsification via a solvent-free process. *AAPS Pharm Sci Tech* 2004; **5**: E24.

21 Authors

MJ Lawrence.

22 Date of Revision

22 August 2005.

Meglumine

1 Nonproprietary Names

BP: Meglumine
JP: Meglumine
PhEur: Megluminum
USP: Meglumine

2 Synonyms

1-Methylamino-1-deoxy-D-glucitol; *N*-methylglucamine; *N*-methyl-D-glucamine.

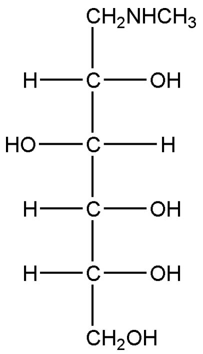
3 Chemical Name and CAS Registry Number

1-Deoxy-1-(methylamino)-D-glucitol [6284-40-8]

4 Empirical Formula and Molecular Weight

$C_7H_{17}NO_5$ 195.21

5 Structural Formula



6 Functional Category

Organic base.

7 Applications in Pharmaceutical Formulation or Technology

Meglumine is an organic base used as a pH-adjusting agent and solubilizing agent primarily in the preparation of soluble salts of iodinated organic acids used as X-ray contrast media.

8 Description

Meglumine occurs as a white to slightly yellow-colored crystalline powder; it is odorless or with a slight odor.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for meglumine.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	—	+	—
Appearance of solution	+	+	+
Melting range 128–132°C		128–131°C	–
Specific optical rotation	−16.0 to −17.0°	−16.0 to −17.0°	−15.7 to −17.3°
Reducing substances	—	≤0.2%	—
Loss on drying	≤0.5%	≤0.5%	≤1.0%
Residue on ignition	≤0.10%	≤0.1%	≤0.1%
Absence of reducing substances	+	—	+
Bacterial endotoxins	—	≤1.5 IU/g	—
Heavy metals	≤10 ppm	≤10 ppm	≤0.002%
Iron	—	≤10 ppm	—
Arsenic	≤1 ppm	—	—
Chloride	≤0.009%	≤100 ppm	—
Sulfate	≤0.019%	≤150 ppm	—
Assay	≥99.0%	99.0–101.0%	99.0–100.5%

10 Typical Properties

Acidity/alkalinity: pH = 10.5 (1% w/v aqueous solution).
Dissociation constant: $pK_a = 9.5$ at 20°C
Melting point: 128–132°C
Osmolarity: a 5.02% w/v aqueous solution is iso-osmotic with serum.
Solubility: *see* Table II.

Table II: Solubility of meglumine.

Solvent	Solubility at 20°C unless otherwise stated
Chloroform	Practically insoluble
Ethanol (95%)	1 in 80 1 in 4.8 at 70°C
Ether	Practically insoluble
Water	1 in 1

Specific rotation $[\alpha]_D^{20}$: −16.5° (10% w/v aqueous solution)

11 Stability and Storage Conditions

Meglumine does not polymerize or dehydrate unless heated above 150°C for prolonged periods.

The bulk material should be stored in a well-closed container in a cool, dry place. Meglumine should not be stored in aluminum containers since it reacts to evolve hydrogen gas; it discolors if stored in containers made from copper or copper alloys. Stainless steel containers are recommended.

12 Incompatibilities

Incompatible with aluminum, copper, mineral acids, and oxidizing materials. Differential scanning calorimeter studies suggest meglumine is incompatible with glipizide.(1)

13 Method of Manufacture

Meglumine is prepared by the imination of glucose and monomethylamine, in an alcoholic solution, followed by catalytic hydrogenation.

14 Safety

Meglumine is widely used in parenteral pharmaceutical formulations and is generally regarded as a nontoxic material at the levels usually employed as an excipient.

LD_{50} (mouse, IP): 1.68 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Meglumine should be handled in a well-ventilated environment and eye protection, gloves, and a respirator are recommended. Exposure to meglumine dust should be kept below 10 mg/m^3 for total inhalable dust (8-hour TWA) or 5 mg/m^3 for respirable dust (8-hour TWA). There is a risk of explosion when meglumine dust is mixed with air.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (injections; oral tablets). Included in parenteral medicines licensed in the UK.

17 Related Substances

Eglumine.

Eglumine

Empirical formula: $C_8H_{19}NO_5$
Molecular weight: 209.24
CAS number: [14216-22-9]
Synonyms: 1-deoxy-1-(ethylamino)-D-glucitol; *N*-ethylglucamine.
Melting point: ≈138°C
Comments: eglumine is prepared similarly to meglumine except that monoethylamine is used as the precursor, instead of monomethylamine.

18 Comments

—

19 Specific References

1 Verma RK, Garg S. Selection of excipients for extended release formulations of glipizide through drug-excipient compatibility testing. *J Pharm Biomed Anal* 2005; **38**: 633–644.

20 General References

Bremecker KD, Seidel K, Böhner A. Polyacrylate gels: use of new bases in drug formulation [in German]. *Dtsch Apoth Ztg* 1990; **130**(8): 401–403.

Chromy V, Kulhanek V, Fischer J. D-(–)-*N*-Methylglucamine buffer for pH 8.5 to 10.5. *Clin Chem* 1978; **24**(2): 379–381.

Chromy V, Zahradnicek L, Voznicek J. Use of *N*-methyl-D-glucamine as buffer in the determination of serum alkaline phosphatase activity. *Clin Chem* 1981; **27**(10): 1729–1732.

Japan Pharmaceutical Excipients Council. *Japanese Pharmaceutical Excipients Directory 1996*. Tokyo: Yakuji Nippon, 1996: 305.

21 Authors

PJ Weller.

22 Date of Revision

11 August 2005.

Menthol

1 Nonproprietary Names

BP: Racementhol
JP: *dl*-Menthol
PhEur: Mentholum racemicum
USP: Menthol

2 Synonyms

Hexahydrothymol; 2-isopropyl-5-methylcyclohexanol; 4-isopropyl-1-methylcyclohexan-3-ol; 3-*p*-menthanol; *p*-menthan-3-ol; *dl*-menthol; peppermint camphor; racemic menthol.

3 Chemical Name and CAS Registry Number

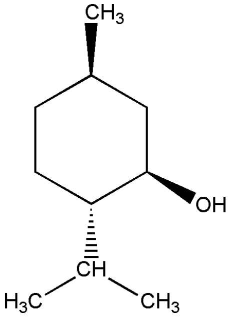
(1*RS*,2*RS*,5*RS*)-(±)-5-Methyl-2-(1-methylethyl)cyclohexanol [15356-70-4]

Note that the following CAS numbers have also been used: [1490-04-6] and [89-78-1].

4 Empirical Formula and Molecular Weight

$C_{10}H_{20}O$ 156.27

5 Structural Formula



6 Functional Category

Flavoring agent; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Menthol is widely used in pharmaceuticals, confectionery, and toiletry products as a flavoring agent or odor enhancer. In addition to its characteristic peppermint flavor, *l*-menthol, which occurs naturally, also exerts a cooling or refreshing sensation that is exploited in many topical preparations. Unlike mannitol, which exerts a similar effect due to a negative heat of solution, *l*-menthol interacts directly with the body's coldness receptors. *d*-Menthol has no cooling effect, while racemic menthol exerts an effect approximately half that of *l*-menthol.

When used to flavor tablets, menthol is generally dissolved in ethanol (95%) and sprayed onto tablet granules and not used as a solid excipient.

Menthol has been investigated as a skin-penetration enhancer and is also used in perfumery, tobacco products, chewing gum and as a therapeutic agent. *See* Table I.

Table I: Uses of menthol.

Use	Concentration (%)
Pharmaceutical products	
Inhalation	0.02–0.05
Oral suspension	0.003
Oral syrup	0.005–0.015
Tablets	0.2–0.4
Topical formulations	0.05–10.0
Cosmetic products	
Toothpaste	0.4
Mouthwash	0.1–2.0
Oral spray	0.3

8 Description

Racemic menthol is a mixture of equal parts of the (1*R*,2*S*,5*R*)- and (1*S*,2*R*,5*S*)-isomers of menthol. It is a free-flowing or agglomerated crystalline powder, or colorless, prismatic, or acicular shiny crystals, or hexagonal or fused masses with a strong characteristic odor and taste. The crystalline form may change with time owing to sublimation within a closed vessel. The USP 28 specifies that menthol may be either naturally occurring *l*-menthol or synthetically prepared racemic or *dl*-menthol. However, the JP 2001 and PhEur 2005, along with other pharmacopeias, include two separate monographs for racemic and *l*-menthol.

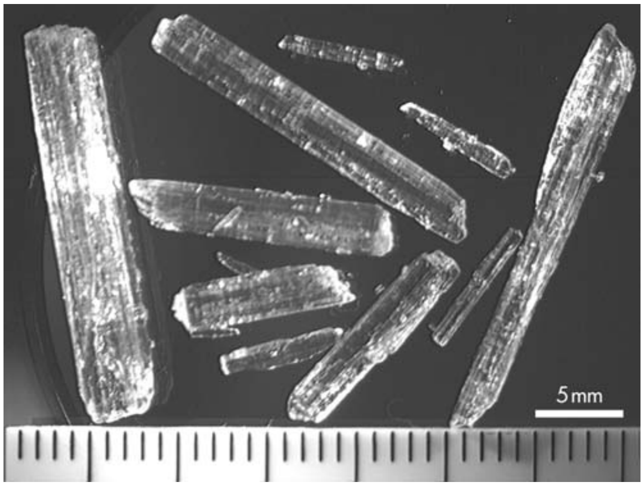


Figure 1: Photomicrograph of large DL-menthol crystals; magnification 7×. Manufacturer: Charkit Chemical Corp., USA.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for menthol.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Acidity or alkalinity	—	+	—
Congealing range	27–28°C	—	+
Melting point			
dl-menthol	—	≈34°C	—
l-menthol	42–44°C	≈43°C	41–44°C
Specific optical rotation			
dl-menthol	−2 to +2°	−0.2 to +0.2°	−2 to +2°
l-menthol	−45 to −51°	—	−45 to −51°
Readily oxidizable substances	—	—	+
Chromatographic purity	—	—	+
Related substances	—	+	—
Appearance of solution	—	+	—
Nonvolatile residue	+	—	⩽0.05%
Residue on evaporation	—	⩽0.05%	—
Organic volatile impurities	—	—	+
Thymol	+	—	—
Nitromethane or nitroethane	+	—	—
Assay	⩾98.0%	—	—

10 Typical Properties

Boiling point: 212°C
Flash point: 91°C
Melting point: 34°C
Refractive index: $n_D^{20} = 1.4615$
Solubility: very soluble in ethanol (95%), chloroform, ether, fatty oils and liquid paraffin; soluble in acetone and benzene; very slightly soluble in glycerin; practically insoluble in water.
Specific gravity: 0.904 at 15°C
Specific rotation $[\alpha]_D^{20}$**:** −2 to +2° (10% w/v alcoholic solution)
See also Section 17.

11 Stability and Storage Conditions

A formulation containing menthol 1% w/w in aqueous cream has been reported to be stable for up to 18 months when stored at room temperature.(1)

Menthol should be stored in a well-closed container at a temperature not exceeding 25°C, since it sublimes readily.

12 Incompatibilities

Incompatible with: butylchloral hydrate; camphor; chloral hydrate; chromium trioxide; β-naphthol; phenol; potassium permanganate; pyrogallol; resorcinol; and thymol.

13 Method of Manufacture

Menthol occurs widely in nature as *l*-menthol and is the principal component of peppermint and cornmint oils obtained from the *Mentha piperita* and *Mentha arvensis* species. Commercially, *l*-menthol is mainly produced by extraction from these volatile oils. It may also be prepared by partial or total synthetic methods.

Racemic menthol is prepared synthetically via a number of routes, e.g. by hydrogenation of thymol.

14 Safety

Almost all toxicological data for menthol relate to its use as a therapeutic agent rather than as an excipient. Inhalation or ingestion of large quantities can result in serious adverse reactions such as ataxia(2) and CNS depression.(3) Although menthol is essentially nonirritant there have been some reports of hypersensitivity following topical application.(4,5) In a Polish study approximately 1% of individuals were determined as being sensitive to menthol.(6)

The WHO has set an acceptable daily intake of menthol at up to 0.4 mg/kg body-weight.(7)

LD_{50} (rat, IM): 10.0 g/kg(8)
LD_{50} (rat, oral): 3.18 g/kg

15 Handling Precautions

May be harmful by inhalation or ingestion in large quantities; may be irritant to the skin, eyes, and mucous membranes. Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (dental preparations, inhalations, oral aerosols, capsules, solutions, suspensions, syrups, and tablets, also topical preparations). Included in nonparenteral medicines licensed in the UK. Accepted for use in foods and confectionery as a flavoring agent of natural origin. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

d-Menthol; *l*-menthol; thymol.

d-Menthol

Empirical formula: $C_{10}H_{20}O$
Molecular weight: 156.27
CAS number: [15356-60-2]
Synonyms: (1*S*,2*R*,5*S*)-(+)-5-methyl-2-(1-methylethyl)cyclohexanol.
Appearance: colorless, prismatic or acicular, shiny crystals, without the characteristic odor, taste, and cooling effect of *l*-menthol. The crystalline form may change with time owing to sublimation within a closed vessel.
Flash point: 91°C
Melting point: 43–44°C
Specific rotation $[\alpha]_D^{23}$**:** +48° (10% w/v alcoholic solution)

l-Menthol

Empirical formula: $C_{10}H_{20}O$
Molecular weight: 156.27
CAS number: [2216-51-5]
Synonyms: levomenthol; levomentholum; (1*R*,2*S*,5*R*)-(–)-5-methyl-2-(1-methylethyl)cyclohexanol.
Appearance: colorless, prismatic, or acicular, shiny crystals, with a strong, characteristic odor, taste, and cooling effect.

The crystalline form may change with time owing to sublimation within a closed vessel.

Flash point: >100°C

Melting point: 41–44°C

Refractive index: $n_D^{20} = 1.4600$

Specific rotation $[\alpha]_D^{20}$**:** −50° (10% w/v alcoholic solution)

Safety:

LD_{50} (mouse, IP): 6.6 g/kg[8]
LD_{50} (mouse, oral): 3.4 g/kg
LD_{50} (rat, IP): 0.7 g/kg
LD_{50} (rat, oral): 3.3 g/kg

18 Comments

It should be noted that considerable variation in the chemical composition of natural menthol oils can occur depending upon their country of origin. The EINECS number for menthol is 201-939-0.

19 Specific References

1 Gallagher P, Jones S. A stability and validation study of 1% w/w menthol in aqueous cream. *Int J Pharm Pract* 1997; **5**: 101–104.
2 Luke E. Addiction to mentholated cigarettes [letter]. *Lancet* 1962; **i**: 110–111.
3 O'Mullane NM, Joyce P, Kamath SV, *et al*. Adverse CNS effects of menthol-containing olabas oil [letter]. *Lancet* 1982; **i**: 1121.
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5 Hayakawa R, Yamamura M, Sugiura M. Contact dermatitis from l-menthol. *Cosmet Toilet* 1996; **111**(7): 28–29.
6 Rudzki E, Kleniewska D. The epidemiology of contact dermatitis in Poland. *Br J Dermatol* 1970; **83**: 543–545.
7 FAO/WHO. Evaluation of certain food additives: Fifty-first report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 2000; No. 891.
8 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 2297.

20 General References

Bauer K, Garbe D, Surburg H. *Common Fragrance and Flavor Materials*. Weinheim: VCH, 1990: 43–46.
Eccles R. Menthol and related cooling compounds. *J Pharm Pharmacol* 1994; **46**: 618–630.
Walker T. Menthol. Properties, uses and some methods of manufacture. *Manuf Chem Aerosol News* 1967; 53.

21 Authors

BA Langdon, MP Mullarney.

22 Date of Revision

26 August 2005.

Methylcellulose

1 Nonproprietary Names

BP: Methylcellulose
JP: Methylcellulose
PhEur: Methylcellulosum
USP: Methylcellulose

2 Synonyms

Benecel; *Culminal MC*; E461; *Methocel*; *Metolose*.

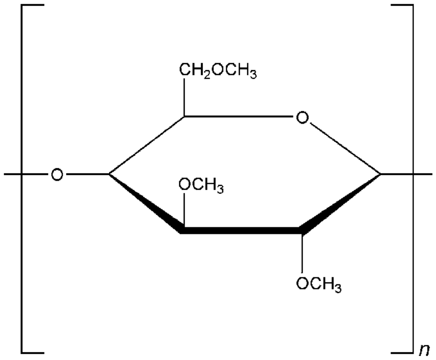
3 Chemical Name and CAS Registry Number

Cellulose methyl ether [9004-67-5]

4 Empirical Formula and Molecular Weight

Methylcellulose is a long-chain substituted cellulose in which approximately 27–32% of the hydroxyl groups are in the form of the methyl ether. The various grades of methylcellulose have degrees of polymerization in the range 50–1000, with molecular weights (number average) in the range 10 000–220 000 Da. The degree of substitution of methylcellulose is defined as the average number of methoxyl (CH_3O) groups attached to each of the anhydroglucose units along the chain. The degree of substitution also affects the physical properties of methylcellulose, such as its solubility.

5 Structural Formula



The structure shown is with complete substitution of the available hydroxyl units of methoxyl substitution. Note that methoxyl substitution can occur at any combination of the hydroxyl groups of the anhydroglucose ring of cellulose at positions 2, 3, and 6. *See* Section 4.

6 Functional Category

Coating agent; emulsifying agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Methylcellulose is widely used in oral and topical pharmaceutical formulations; *see* Table I.

In tablet formulations, low- or medium-viscosity grades of methylcellulose are used as binding agents, the methylcellulose being added either as a dry powder or in solution.(1–3) High-viscosity grades of methylcellulose may also be incorporated in tablet formulations as a disintegrant.(4) Methylcellulose may be added to a tablet formulation to produce sustained-release preparations.(5)

Tablet cores may also be spray-coated with either aqueous or organic solutions of highly substituted low-viscosity grades of methylcellulose to mask an unpleasant taste or to modify the release of a drug by controlling the physical nature of the granules.(6) Methylcellulose coats are also used for sealing tablet cores prior to sugar coating.

Low-viscosity grades of methylcellulose are used to emulsify olive, peanut, and mineral oils.(7) They are also used as suspending or thickening agents for orally administered liquids, methylcellulose commonly being used in place of sugar-based syrups or other suspension bases.(8) Methylcellulose delays the settling of suspensions and increases the contact time of drugs, such as antacids, in the stomach.

High-viscosity grades of methylcellulose are used to thicken topically applied products such as creams and gels.

In ophthalmic preparations, a 0.5–1.0% w/v solution of a highly substituted, high-viscosity grade of methylcellulose has been used as a vehicle for eye drops.(9) However, hypromellose-based formulations are now preferred for ophthalmic preparations.

Therapeutically, methylcellulose is used as a bulk laxative; it has also been used to aid appetite control in the management of obesity, but there is little evidence supporting its efficacy.

Table I: Uses of methylcellulose.

Use	Concentration (%)
Bulk laxative	5.0–30.0
Creams, gels, and ointments	1.0–5.0
Emulsifying agent	1.0–5.0
Ophthalmic preparations	0.5–1.0
Suspensions	1.0–2.0
Sustained-release tablet matrix	5.0–75.0
Tablet binder	1.0–5.0
Tablet coating	0.5–5.0
Tablet disintegrant	2.0–10.0

8 Description

Methylcellulose occurs as a white, fibrous powder or granules. It is practically odorless and tasteless. It should be labeled to indicate its viscosity type (viscosity of a 1 in 50 solution).

9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Acidity/alkalinity: pH = 5.5–8.0 for a 1% w/v aqueous suspension.

Table II: Pharmacopeial specifications for methylcellulose.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	—	+	—
Appearance of solution	+	+	—
pH	5.0–8.0	5.5–8.0	—
Apparent viscosity	+	+	+
Arsenic	⩽2 ppm	—	—
Loss on drying	⩽5.0%	⩽10.0%	⩽5.0%
Residue on ignition	⩽1.0%	⩽1.0%	⩽1.5%
Chlorides	⩽0.284%	⩽0.5%	—
Iron	⩽100 ppm	—	—
Heavy metals	⩽10 ppm	⩽20 ppm	⩽0.001%
Organic volatile impurities	—	—	+
Assay (of methoxyl groups)	26.0–33.0%	—	27.5–31.5%

Angle of repose: 40–50°
Autoignition temperature: ≈360°C
Degree of substitution: 1.64–1.92
Density (bulk): 0.276 g/cm^3
Density (tapped): 0.464 g/cm^3
Density (true): 1.341 g/cm^3
Melting point: begins to brown at 190–200°C; begins to char at 225–230°C.
Refractive index of solution:
$n_D^{20} = 1.336$ (2% aqueous solution).
Solubility: practically insoluble in acetone, methanol, chloroform, ethanol (95%), ether, saturated salt solutions, toluene, and hot water. Soluble in glacial acetic acid and in a mixture of equal volumes of ethanol and chloroform. In cold water, methylcellulose swells and disperses slowly to form a clear to opalescent, viscous, colloidal dispersion.
Surface tension:
53–59 mN/m (53–59 dynes/cm) for a 0.05% w/v solution at 25°C;
45–55 mN/m for 0.1% at 20°C.

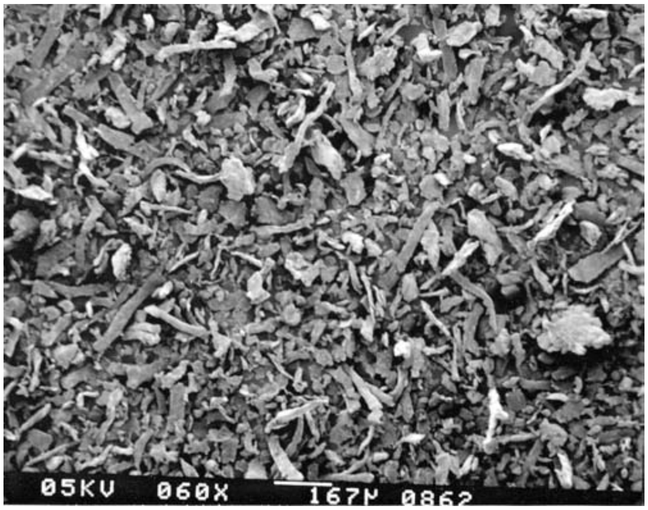
Interfacial tension of solution versus paraffin oil is 19–23 mN/m for 0.1% w/v solution at 20°C.

Viscosity (dynamic): various grades of methylcellulose are commercially available that vary in their degree of polymerization. Aqueous solutions at concentrations of 2% w/v will produce viscosities between 5 and 75 000 mPa s. Individual grades of methylcellulose have a stated, narrowly defined viscosity range measured for a 2% w/v solution. The viscosity of solutions may be increased by increasing the concentration of methylcellulose. Increased temperatures reduce the viscosity of solutions until gel formation occurs at 50–60°C. The process of thermogelation is reversible, with a viscous solution being reformed on cooling. *See also* Table III.

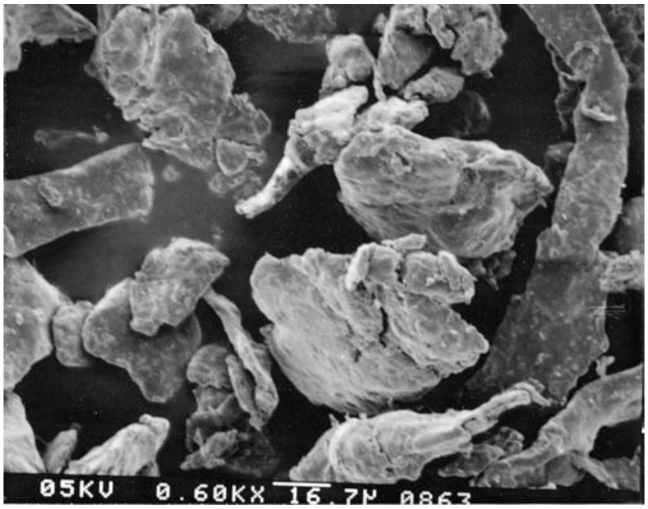
Table III: Typical viscosity values for 2% w/v aqueous solutions of *Methocel* (Dow Chemical Co.) at 20°C.

Methocel grade	Viscosity (mPa s)
A4MP	4000
A15-LV	15
A15CP	1500
A4CP	400

SEM: 1
Excipient: Methylcellulose
Manufacturer: Dow Chemical Co.
Lot No.: KC16012N21
Magnification: 60×



SEM: 2
Excipient: Methylcellulose
Manufacturer: Dow Chemical Co.
Lot No.: KC16012N21
Magnification: 600×



11 Stability and Storage Conditions

Methylcellulose powder is stable, although slightly hygroscopic. The bulk material should be stored in an airtight container in a cool, dry place.

Solutions of methylcellulose are stable to alkalis and dilute acids at pH 3–11, at room temperature. At pH less than 3, acid-catalyzed hydrolysis of the glucose–glucose linkages occurs and the viscosity of methylcellulose solutions is reduced.(10) On heating, solution viscosity is reduced until gel formation occurs at approximately 50°C; *see* Section 10.

Methylcellulose solutions are liable to microbial spoilage and antimicrobial preservatives should therefore be used.

Solutions may also be sterilized by autoclaving, although this process can decrease the viscosity of a solution.(11,12) The change in viscosity after autoclaving is related to solution pH. Solutions at pH less than 4 had viscosities reduced by more than 20% subsequent to autoclaving.(11)

12 Incompatibilities

Methylcellulose is incompatible with aminacrine hydrochloride; chlorocresol; mercuric chloride; phenol; resorcinol; tannic acid; silver nitrate; cetylpyridinium chloride; *p*-hydroxybenzoic acid; *p*-aminobenzoic acid; methylparaben; propylparaben; and butylparaben.

Salts of mineral acids (particularly polybasic acids), phenols, and tannins will coagulate solutions of methylcellulose, although this can be prevented by the addition of ethanol (95%) or glycol diacetate. Complexation of methylcellulose occurs with highly surface-active compounds such as tetracaine and dibutoline sulfate.

High concentrations of electrolytes increase the viscosity of methylcellulose mucilages owing to the 'salting out' of methylcellulose. With very high concentrations of electrolytes, the methylcellulose may be completely precipitated in the form of a discrete or continuous gel. Methylcellulose is incompatible with strong oxidizing agents.

13 Method of Manufacture

Methylcellulose is prepared from wood pulp (cellulose) by treatment with alkali followed by methylation of the alkali cellulose with methyl chloride. The product is then purified and ground to powder form.

14 Safety

Methylcellulose is widely used in a variety of oral and topical pharmaceutical formulations. It is also extensively used in cosmetics and food products and is generally regarded as a nontoxic, nonallergenic, and nonirritant material.(13)

Following oral consumption, methylcellulose is not digested or absorbed and is therefore a noncaloric material. Ingestion of excessive amounts of methylcellulose may temporarily increase flatulence and gastrointestinal distension.

In the normal individual, oral consumption of large amounts of methylcellulose has a laxative action and medium- or high-viscosity grades are therefore used as bulk laxatives.

Esophageal obstruction may occur if methylcellulose is swallowed with an insufficient quantity of liquid. Consumption of large quantities of methylcellulose may additionally interfere with the normal absorption of some minerals. However, this and the other adverse effects discussed above relate mainly to the use of methylcellulose as a bulk laxative and are not significant factors when methylcellulose is used as an excipient in oral preparations.

Methylcellulose is not commonly used in parenteral products, although it has been used in intra-articular and intramuscular injections. Studies in rats have suggested that parenterally administered methylcellulose may cause glomerulonephritis and hypertension.(13)

The WHO has not specified an acceptable daily intake of methylcellulose since the level of use in foods was not considered to be a hazard to health.(14)

LD_{50} (mouse, IP): 275 g/kg(15)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Dust may be irritant to the eyes and eye protection should be worn. Excessive dust generation should be avoided to minimize the risk of explosion. Methylcellulose is combustible. Spills of the dry powder or solution should be cleaned up immediately, as the slippery film that forms can be dangerous.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (sublingual tablets; IM injections; nasal preparations; ophthalmic preparations; oral capsules, oral suspensions, and oral tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Ethylcellulose; hydroxyethyl cellulose; hydroxyethylmethyl cellulose; hypromellose.

18 Comments

The thermal gelation temperature for methylcellulose decreases as a function of concentration. The presence of additives can increase or decrease the thermal gelation temperature. The presence of drugs can influence the properties of methylcellulose gels.(16) In addition, the viscosity of methylcellulose solutions can be modified by the presence of drugs or other additives.(17) Aqueous solutions of methylcellulose can be frozen and do not undergo phase separation upon freezing.

Methylcellulose is best dissolved in water by one of three methods, the most suitable being chosen for a particular application.

The most commonly used method is to add methylcellulose initially to hot water. The appropriate quantity of methylcellulose required to produce a solution of specified viscosity is mixed with water at 70°C; about half the desired final volume of water is used. Cold water or ice is then added to the hot methylcellulose slurry in order to reduce the temperature to below 20°C. A clear, aqueous methylcellulose solution is obtained.

Alternatively, either methylcellulose powder may be dry-blended with another powder prior to mixing with cold water, or methylcellulose powder may be moistened with an organic solvent such as ethanol (95%) prior to the addition of water.

In general, methylcellulose solutions exhibit pseudoplastic flow and there is no yield point. Nonthixotropic flow properties are observed below the gelation temperature.

Note that some cellulose ether products possess hydroxypropyl substitutions in addition to methyl substitutions but are designated with the same trade name in a product line, differing only by a unique identifier code. These products should not be confused with the products that contain only methyl substitutions. A specification for methylcellulose is contained in the Food Chemicals Codex (FCC).

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21 Authors

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22 Date of Revision

9 August 2005.

Methylparaben

1 Nonproprietary Names

BP: Methyl hydroxybenzoate
JP: Methyl parahydroxybenzoate
PhEur: Methylis parahydroxybenzoas
USPNF: Methylparaben

2 Synonyms

E218; 4-hydroxybenzoic acid methyl ester; methyl *p*-hydroxybenzoate; *Nipagin M*; *Uniphen P-23*.

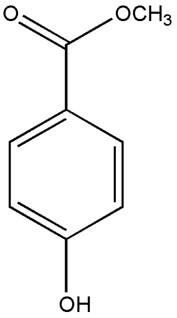
3 Chemical Name and CAS Registry Number

Methyl-4-hydroxybenzoate [99-76-3]

4 Empirical Formula and Molecular Weight

$C_8H_8O_3$ 152.15

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

Methylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations; *see* Table I. It may be used either alone or in combination with other parabens or with other antimicrobial agents. In cosmetics, methylparaben is the most frequently used antimicrobial preservative.$^{(1)}$

The parabens are effective over a wide pH range and have a broad spectrum of antimicrobial activity, although they are most effective against yeasts and molds. Antimicrobial activity increases as the chain length of the alkyl moiety is increased, but aqueous solubility decreases; therefore a mixture of parabens is frequently used to provide effective preservation. Preservative efficacy is also improved by the addition of propylene glycol (2–5%), or by using parabens in combination with other antimicrobial agents such as imidurea; *see* Section 10.

Owing to the poor solubility of the parabens, paraben salts (particularly the sodium salt) are more frequently used in formulations. However, this raises the pH of poorly buffered formulations.

Methylparaben (0.18%) together with propylparaben (0.02%) has been used for the preservation of various parenteral pharmaceutical formulations; *see* Section 14.

Table I: Uses of methylparaben.

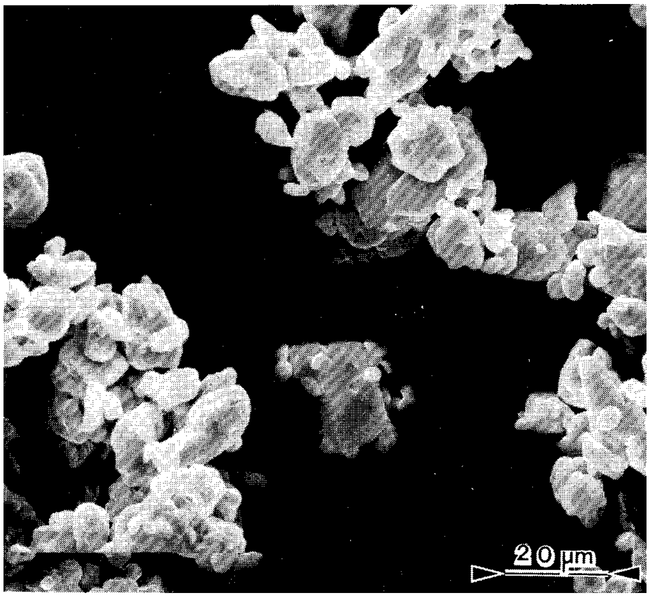
Use	Concentration (%)
IM, IV, SC injections(a)	0.065–0.25
Inhalation solutions	0.025–0.07
Intradermal injections	0.10
Nasal solutions	0.033
Ophthalmic preparations(a)	0.015–0.2
Oral solutions and suspensions	0.015–0.2
Rectal preparations	0.1–0.18
Topical preparations	0.02–0.3
Vaginal preparations	0.1–0.18

(a) *See* Section 14.

8 Description

Methylparaben occurs as colorless crystals or a white crystalline powder. It is odorless or almost odorless and has a slight burning taste.

SEM: 1
Excipient: Methylparaben
Supplier: Bate Chemical Co. Ltd.
Magnification: 600×



9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for methylparaben.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Appearance of solution	—	+	+
Acidity	—	+	+
Heavy metals	≤20 ppm	—	—
Impurities	—	+	+
Loss on drying	≤0.5%	—	—
Parahydroxybenzoic acid	+	—	—
Chlorides	≤0.035%	—	—
Melting range	—	—	125–128°C
Readily carbonizable substances	+	—	+
Organic volatile impurities	—	—	+
Related substances	—	+	—
Residue on ignition	≤0.10%	≤0.1%	≤0.1%
Assay (dried basis)	≥99.0%	98.0–102.0%	99.0–100.5%

10 Typical Properties

Antimicrobial activity: *see* Table III. Methylparaben exhibits antimicrobial activity of pH 4–8. Preservative efficacy decreases with increasing pH owing to the formation of the phenolate anion. Parabens are more active against yeasts and molds than against bacteria. They are also more active against Gram-positive bacteria than against Gram-negative bacteria.

Table III: Minimum inhibitory concentrations (MICs) of methylparaben in aqueous solution.[4]

Microorganism	MIC (μg/mL)
Aerobacter aerogenes ATCC 8308	2000
Aspergillus oryzae	600
Aspergillus niger ATCC 9642	1000
Aspergillus niger ATCC 10254	1000
Bacillus cereus var. *mycoides* ATCC 6462	2000
Bacillus subtilis ATCC 6633	2000
Candida albicans ATCC 10231	2000
Enterobacter cloacae ATCC 23355	1000
Escherichia coli ATCC 8739	1000
Escherichia coli ATCC 9637	1000
Klebsiella pneumoniae ATCC 8308	1000
Penicillium chrysogenum ATCC 9480	500
Penicillium digitatum ATCC 10030	500
Proteus vulgaris ATCC 8427	2000
Proteus vulgaris ATCC 13315	1000
Pseudomonas aeruginosa ATCC 9027	4000
Pseudomonas aeruginosa ATCC 15442	4000
Pseudomonas stutzeri	2000
Rhizopus nigricans ATCC 6227A	500
Saccharomyces cerevisiae ATCC 9763	1000
Salmonella typhosa ATCC 6539	1000
Sarcina lutea	4000
Serratia marcescens ATCC 8100	1000
Staphylococcus aureus ATCC 6538P	2000
Staphylococcus epidermidis ATCC 12228	2000
Trichoderma lignorum ATCC 8678	250
Trichoderma mentagrophytes	250

Methylparaben is the least active of the parabens; antimicrobial activity increases with increasing chain length of the alkyl moiety. Activity may be improved by using combinations of parabens as synergistic effects occur. Therefore, combinations of methyl-, ethyl-, propyl-, and butylparaben are often used together. Activity has also been reported to be enhanced by the addition of other excipients such as: propylene glycol (2–5%);(2) phenylethyl alcohol;(3) and edetic acid.(4) Activity may also be enhanced owing to synergistic effects by using combinations of parabens with other antimicrobial preservatives such as imidurea.(5)

The hydrolysis product *p*-hydroxybenzoic acid has practically no antimicrobial activity.

See also Section 12.

Density (true): 1.352 g/cm^3

Dissociation constant: pK_a = 8.4 at 22°C

Melting point: 125–128°C

Partition coefficients: values for different vegetable oils vary considerably and are affected by the purity of the oil; *see* Table IV.

Solubility: *see* Table V.

Table IV: Partition coefficients of methylparaben in vegetable oil and water.[6,7]

Solvent	Partition coefficient oil : water
Almond oil	7.5
Castor oil	6.0
Corn oil	4.1
Diethyl adipate	200
Isopropyl myristate	18.0
Lanolin	7.0
Mineral oil	0.1
Peanut oil	4.2
Soybean oil	6.1

Table V: Solubility of methylparaben in various solvents.[4]

Solvent	Solubility at 25°C unless otherwise stated
Ethanol	1 in 2
Ethanol (95%)	1 in 3
Ethanol (50%)	1 in 6
Ether	1 in 10
Glycerin	1 in 60
Mineral oil	Practically insoluble
Peanut oil	1 in 200
Propylene glycol	1 in 5
Water	1 in 400 1 in 50 at 50°C 1 in 30 at 80°C

11 Stability and Storage Conditions

Aqueous solutions of methylparaben at pH 3–6 may be sterilized by autoclaving at 120°C for 20 minutes, without decomposition.(8) Aqueous solutions at pH 3–6 are stable (less than 10% decomposition) for up to about 4 years at room temperature, while aqueous solutions at pH 8 or above are subject to rapid hydrolysis (10% or more after about 60 days storage at room temperature); *see* Tables VI and VII.(9)

Methylparaben should be stored in a well-closed container in a cool, dry place.

Table VI: Predicted rate constants and half-lives for methylparaben dissolved in dilute hydrochloric acid solution, at 25°C.

Initial pH of solution	Rate constant $k \pm \sigma^{(a)}$ (hour^{-1})	Half-life $t_{1/2} \pm \sigma^{(a)}$ (day)
1	$(1.086 \pm 0.005) \times 10^{-4}$	266 ± 13
2	$(1.16 \pm 0.12) \times 10^{-5}$	2490 ± 260
3	$(6.1 \pm 1.5) \times 10^{-7}$	47000 ± 12000
4	$(3.27 \pm 0.64) \times 10^{-7}$	88000 ± 17000

(a) Indicates the standard error.

Table VII: Predicted remaining amount of methylparaben dissolved in dilute hydrocholoric acid solution, after autoclaving.

Initial pH of solution	Rate constant $k \pm \sigma^{(a)}$ (hour^{-1})	Predicted residual amount after autoclaving (%)
1	$(4.96 \pm 0.16) \times 10^{-1}$	84.77 ± 0.46
2	$(4.49 \pm 0.37) \times 10^{-2}$	98.51 ± 0.12
3	$(2.79 \pm 0.57) \times 10^{-3}$	99.91 ± 0.02
4	$(1.49 \pm 0.22) \times 10^{-3}$	99.95 ± 0.01

(a) Indicates the standard error.

12 Incompatibilities

The antimicrobial activity of methylparaben and other parabens is considerably reduced in the presence of nonionic surfactants, such as polysorbate 80, as a result of micellization.(10,11) However, propylene glycol (10%) has been shown to potentiate the antimicrobial activity of the parabens in the presence of nonionic surfactants and prevents the interaction between methylparaben and polysorbate 80.(12)

Incompatibilities with other substances, such as bentonite,(13) magnesium trisilicate,(14) talc, tragacanth,(15) sodium alginate,(16) essential oils,(17) sorbitol,(18) and atropine,(19) have been reported. It also reacts with various sugars and related sugar alcohols.(20)

Absorption of methylparaben by plastics has also been reported; the amount absorbed is dependent upon the type of plastic and the vehicle. It has been claimed that low-density and high-density polyethylene bottles do not absorb methylparaben.(21)

Methylparaben is discolored in the presence of iron and is subject to hydrolysis by weak alkalis and strong acids.

13 Method of Manufacture

Methylparaben is prepared by the esterification of *p*-hydroxybenzoic acid with methanol.

14 Safety

Methylparaben and other parabens are widely used as antimicrobial preservatives in cosmetics and oral and topical pharmaceutical formulations. Although parabens have also been used as preservatives in injections and ophthalmic preparations, they are now generally regarded as being unsuitable for these types of formulations owing to the irritant potential of the parabens. These experiences may depend on immune responses to enzymatically formed metabolites of the parabens in the skin.

Parabens are nonmutagenic, nonteratogenic, and noncarcinogenic. Sensitization to the parabens is rare, and these compounds do not exhibit significant levels of photocontact sensitization or phototoxicity.

Hypersensitivity reactions to parabens, generally of the delayed type and appearing as contact dermatitis, have been reported. However, given the widespread use of parabens as preservatives, such reactions are relatively uncommon; the classification of parabens in some sources as high-rate sensitizers may be overstated.(22)

Immediate hypersensitivity reactions following injection of preparations containing parabens have also been reported.(23–25) Delayed-contact dermatitis occurs more frequently when parabens are used topically, but has also been reported to occur after oral administration.(26–28)

Unexpectedly, preparations containing parabens may be used by patients who have reacted previously with contact dermatitis provided they are applied to another, unaffected, site. This has been termed the paraben paradox.(29)

Concern has been expressed over the use of methylparaben in infant parenteral products because bilirubin binding may be affected, which is potentially hazardous in hyperbilirubinemic neonates.(30)

The WHO has set an estimated total acceptable daily intake for methyl-, ethyl-, and propylparabens at up to 10 mg/kg body-weight.(31)

LD_{50} (dog, oral): 3.0 g/kg(32)
LD_{50} (mouse, IP): 0.96 g/kg
LD_{50} (mouse, SC): 1.20 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Methylparaben may be irritant to the skin, eyes, and mucous membranes and should be handled in a well-ventilated environment. Eye protection, gloves, and a dust mask or respirator are recommended.

16 Regulatory Status

Methylparaben and propylparaben are affirmed GRAS Direct Food Substances in the USA at levels up to 0.1%. All esters except the benzyl ester are allowed for injection in Japan. In cosmetics, the EU and Brazil allow use of each paraben at 0.4%, but the total of all parabens may not exceed 0.8%. The upper limit in Japan is 1.0%.

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IM, IV, and SC injections; inhalation preparations; ophthalmic preparations; oral capsules, tablets, solutions and suspensions; otic, rectal, topical, and vaginal preparations). Included in medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Butylparaben; ethylparaben; methylparaben potassium; methylparaben sodium; propylparaben.

Methylparaben potassium

Empirical formula: $C_8H_7KO_3$
Molecular weight: 190.25
CAS number: [26112-07-2]

Synonyms: methyl 4-hydroxybenzoate potassium salt; potassium methyl hydroxybenzoate.
Comments: methylparaben potassium may be used instead of methylparaben because of its greater aqueous solubility.

Methylparaben sodium
Empirical formula: $C_8H_7NaO_3$
Molecular weight: 174.14
CAS number: [5026-62-0]
Synonyms: E219; methyl 4-hydroxybenzoate sodium salt; sodium methyl hydroxybenzoate; soluble methyl hydroxybenzoate.
Appearance: a white, odorless or almost odorless, hygroscopic crystalline powder.
Acidity/alkalinity: pH = 9.5–10.5 (0.1% w/v aqueous solution)
Solubility: 1 in 50 of ethanol (95%); 1 in 2 of water; practically insoluble in fixed oils.
Comments: methylparaben sodium may be used instead of methylparaben because of its greater aqueous solubility. However, it may cause the pH of a formulation to become more alkaline.

18 Comments

The EINECS number for methylparaben is 202-785-7. In addition to the most commonly used paraben esters, some other less-common esters have also been used; *see* Table VIII. A specification for methylparaben is contained in the Food Chemicals Codex (FCC).

Table VIII: CAS numbers of less common paraben esters.

Name	CAS Number
Benzylparaben	94-18-8
Isobutylparaben	4247-02-3
Isopropylparaben	4191-73-5

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21 Authors

R Johnson, R Steer.

22 Date of Revision

23 August 2005.

Mineral Oil

1 Nonproprietary Names

BP: Liquid paraffin
JP: Liquid paraffin
PhEur: Paraffinum liquidum
USP: Mineral oil

2 Synonyms

Avatech; *Drakeol*; heavy mineral oil; heavy liquid petrolatum; liquid petrolatum; paraffin oil; *Sirius*; white mineral oil.

3 Chemical Name and CAS Registry Number

Mineral oil [8012-95-1]

4 Empirical Formula and Molecular Weight

Mineral oil is a mixture of refined liquid saturated aliphatic (C_{14}–C_{18}) and cyclic hydrocarbons obtained from petroleum.

5 Structural Formula

See Section 4.

6 Functional Category

Emollient; lubricant; oleaginous vehicle; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Mineral oil is used primarily as an excipient in topical pharmaceutical formulations, where its emollient properties are exploited as an ingredient in ointment bases; *see* Table I. It is additionally used in oil-in-water emulsions,(1–5) as a solvent, and as a lubricant in capsule and tablet formulations, and to a limited extent as a mold-release agent for cocoa butter suppositories. It has also been used in the preparation of microspheres.(6–8)

Therapeutically, mineral oil has been used as a laxative, *see* Section 14. It is indigestible and thus has limited absorption. Mineral oil is used in ophthalmic formulations for its lubricant properties. It is also used in cosmetics and some food products.(9)

Table I: Uses of mineral oil.

Use	Concentration (%)
Ophthalmic ointments	3.0–60.0
Otic preparations	0.5–3.0
Topical emulsions	1.0–32.0
Topical lotions	1.0–20.0
Topical ointments	0.1–95.0

8 Description

Mineral oil is a transparent, colorless, viscous oily liquid, without fluorescence in daylight. It is practically tasteless and odorless when cold, and has a faint odor of petroleum when heated.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for mineral oil.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	—
Specific gravity	0.860–0.890	0.827–0.890	0.845–0.905
Viscosity	$\geqslant 37\ \mathrm{mm^2/s}$[a]	110–230 mPa s[b]	$\geqslant 34.5\ \mathrm{mm^2/s}$[c]
Odor	+	—	—
Acidity or alkalinity	+	+	+
Heavy metals	$\leqslant$10 ppm	—	—
Arsenic	$\leqslant$2 ppm	—	—
Solid paraffin	+	+	+
Sulfur compounds	+	—	—
Polycyclic aromatic compounds	+	+	—
Limit of polynuclear compounds	+	—	+
Readily carbonizable substances	+	+	+

[a] At 37.8°C.
[b] At 20°C.
[c] At 40°C.

10 Typical Properties

Boiling point: $>360°C$
Flash point: 210–224°C
Pour point: -12.2 to -9.4°C
Refractive index: n_D^{20} = 1.4756–1.4800
Surface tension: ≈ 35 mN/m at 25°C.
Solubility: practically insoluble in ethanol (95%), glycerin, and water; soluble in acetone, benzene, chloroform, carbon disulfide, ether, and petroleum ether. Miscible with volatile oils and fixed oils, with the exception of castor oil.
Viscosity (dynamic): 110–230 mPa s at 20°C.

11 Stability and Storage Conditions

Mineral oil undergoes oxidation when exposed to heat and light. Oxidation begins with the formation of peroxides, exhibiting an 'induction period'. Under ordinary conditions, the induction period may take months or years. However, once a trace of peroxide is formed, further oxidation is autocatalytic and proceeds very rapidly. Oxidation results in the formation of aldehydes and organic acids, which impart taste and odor. Stabilizers may be added to retard oxidation; butylated hydroxyanisole, butylated hydroxytoluene, and alpha tocopherol are the most commonly used antioxidants.

Mineral oil may be sterilized by dry heat.

Mineral oil should be stored in an airtight container, protected from light, in a cool, dry place.

12 Incompatibilities

Incompatible with strong oxidizing agents.

13 Method of Manufacture

Mineral oil is obtained by distillation of petroleum. The lighter hydrocarbons are first removed by distillation and the residue is then redistilled between 330–390°C. The distillate is chilled and the solid fractions are removed by filtration. The filtrate is then further purified and decolorized by high-pressure hydrogenation or sulfuric acid treatment; the purified filtrate is then filtered through adsorbents. The liquid portion obtained is distilled and the portion boiling below 360°C is discarded. A suitable stabilizer may be added to the mineral oil; *see* Section 11.

14 Safety

Mineral oil is used as an excipient in a wide variety of pharmaceutical formulations; *see* Section 16. It is also used in cosmetics and in some food products.

Therapeutically, mineral oil has been used in the treatment of constipation, as it acts as a lubricant and stool softener when taken orally. Daily doses of up to 45 mL have been administered orally, while doses of up to 120 mL have been used as an enema. However, excessive dosage of mineral oil, either orally or rectally, can result in anal seepage and irritation and its oral use as a laxative is not considered desirable.

Chronic oral consumption of mineral oil may impair the appetite and interfere with the absorption of fat-soluble vitamins. Prolonged use should be avoided. Mineral oil is absorbed to some extent when emulsified and can lead to granulomatous reactions. Similar reactions also occur upon injection of the oil;(10) injection may also cause vasospasm.

The most serious adverse reaction to mineral oil is lipoid pneumonia caused by aspiration of the oil.(11,12) Mineral oil can enter the bronchial tree without eliciting the cough reflex.(13) With the reduction in the use of mineral oil in nasal formulations, the incidence of lipoid pneumonia has been greatly reduced. However, lipoid pneumonia has also been associated with the use of mineral oil-containing cosmetics(14) and ophthalmic preparations.(15) It is recommended that products containing mineral oil not be used in very young children, the elderly, or persons with debilitating illnesses.

Given its widespread use in many topical products, mineral oil has been associated with few instances of allergic reactions.

The WHO has not specified an acceptable daily intake of mineral oil given the low concentration consumed in foods.(16)

LD_{50} (mouse, oral): 22 g/kg(17)

15 Handling Precautions

Observe precautions appropriate to the circumstances and quantity of material handled. Avoid inhalation of vapors and wear protective clothing to prevent skin contact. Mineral oil is combustible.

16 Regulatory Status

GRAS listed. Accepted in the UK for use in certain food applications. Included in the FDA Inactive Ingredients Guide (dental preparations, IV injections, ophthalmic preparations, oral capsules and tablets, otic, topical, transdermal, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Mineral oil and lanolin alcohols; light mineral oil; paraffin; petrolatum.

18 Comments

Mineral oil in completely filled soft plastic tubes showed bubbles of gas after gamma irradiation. The bubbles were larger at higher levels of radiation. The iodine value also increased after high and low levels of irradiation.

19 Specific References

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21 Authors

SC Owen.

22 Date of Revision

17 August 2005.

Mineral Oil, Light

1 Nonproprietary Names

BP: Light liquid paraffin
JP: Light liquid paraffin
PhEur: Paraffinum perliquidum
USPNF: Light mineral oil

2 Synonyms

905 (mineral hydrocarbons); *Citation*; light liquid petrolatum; light white mineral oil.

3 Chemical Name and CAS Registry Number

Light mineral oil [8012-95-1]

4 Empirical Formula and Molecular Weight

Light mineral oil is a mixture of refined liquid saturated hydrocarbons obtained from petroleum. It is less viscous and has a lower specific gravity than mineral oil.

5 Structural Formula

A mixture of refined liquid hydrocarbons, essentially paraffins and naphthenic in nature, obtained from petroleum.

6 Functional Category

Emollient; oleaginous vehicle; solvent; tablet and capsule lubricant; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Light mineral oil is used in applications similar to those of mineral oil. It is used primarily as an excipient in topical pharmaceutical formulations where its emollient properties are exploited in ointment bases;(1–3) *see* Table I. It is also used in ophthalmic formulations.(4,5) Light mineral oil is additionally used in oil-in-water and polyethlylene glycol/gylcerol emulsions;(6–9) as a solvent and lubricant in capsules and tablets; as a solvent and penetration enhancer in transdermal preparations;(10) and as the oily medium used in the microencapsulation of many drugs.(11–20)

Light mineral oil is also used in cosmetics and certain food products.

Table I: Uses of light mineral oil.

Use	Concentration (%)
Ophthalmic ointments	$\leqslant 15.0$
Otic preparations	$\leqslant 50.0$
Topical emulsions	1.0–20.0
Topical lotions	7.0–16.0
Topical ointments	0.2–23.0

8 Description

Light mineral oil is a transparent, colorless liquid, without fluorescence in daylight. It is practically tasteless and odorless when cold, and has a faint odor when heated. The USPNF 23 specifies that light mineral oil may contain a suitable stabilizer.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for light mineral oil.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	—
Specific gravity	0.830–0.870	0.810–0.875	0.818–0.880
Viscosity	$\leqslant 37\ \mathrm{mm^2/s}$[a]	25–80 mPa s	$\leqslant 33.5\ \mathrm{mm^2/s}$[b]
Acidity or alkalinity	+	+	—
Heavy metals	$\leqslant 10$ ppm	—	—
Arsenic	$\leqslant 2$ ppm	—	—
Sulfur compounds	+	—	—
Readily carbonizable substances	+	+	+
Polycyclic aromatic compounds	+	+	—
Limit of polynuclear compounds	—	—	+
Odor	+	—	—
Solid paraffin	+	+	+

[a] At 37.8°C.
[b] At 40°C.

10 Typical Properties

Solubility: soluble in chloroform, ether, and hydrocarbons; sparingly soluble in ethanol (95%); practically insoluble in water.

11 Stability and Storage Conditions

Light mineral oil undergoes oxidation when exposed to heat and light. Oxidation begins with the formation of peroxides, exhibiting an 'induction period'. Under typical storage conditions, the induction period may take months or years. However, once a trace of peroxide is formed, further oxidation is autocatalytic and proceeds very rapidly. Oxidation results in the formation of aldehydes and organic acids, which impart taste and odor. The USPNF 23 permits the addition of suitable stabilizers to retard oxidation, butylated hydroxyanisole, butylated hydroxytoluene, and alpha tocopherol being the most commonly used antioxidants.

Light mineral oil may be sterilized by dry heat.

Light mineral oil should be stored in an airtight container in a cool, dry place and protected from light.

12 Incompatibilities

Incompatible with strong oxidizing agents.

13 Method of Manufacture

Light mineral oil is obtained by the distillation of petroleum. A suitable stabilizer may be added to the oil; *see* Section 11.

See also Mineral Oil for further information.

14 Safety

Light mineral oil is used in applications similar to those of mineral oil. Mineral oil is considered safe by the FDA for direct use in foods. However, oral ingestion of large doses of light mineral oil or chronic consumption may be harmful. Chronic use may impair appetite and interfere with the absorption of fat-soluble vitamins. It is absorbed to some extent when emulsified, leading to granulomatous reactions. Oral and intranasal use of mineral oil or products containing mineral oil by infants or children is not recommended because of the possible danger of causing lipoid pneumonia.

See Mineral Oil for further information.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Since light mineral oil is combustible, it should not be handled or stored near heat, sparks, or flame. Light mineral oil should not be mixed with or stored with strong oxidants. Inhalation of mineral oil vapors may be harmful.

16 Regulatory Status

GRAS listed. Accepted in the UK for use in certain food applications. Light mineral oil is included in the FDA Inactive Ingredients Guide (ophthalmic preparations, oral capsules and tablets, otic, rectal, topical, and transdermal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Mineral oil; mineral oil and lanolin alcohols; paraffin; petrolatum.

18 Comments

—

19 Specific References

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See also Mineral Oil.

21 Authors

SC Owen.

22 Date of Revision

11 August 2005.

Mineral Oil and Lanolin Alcohols

1 Nonproprietary Names

None adopted.

2 Synonyms

Amerchol L-101; liquid paraffin and lanolin alcohols; *Protalan M-16*; *Protalan M-26*.

3 Chemical Name and CAS Registry Number

Mineral oil [8012-95-1]
Lanolin alcohols [8027-33-6]

4 Empirical Formula and Molecular Weight

A mixture of mineral oil and lanolin alcohols.

5 Structural Formula

See Section 4.

6 Functional Category

Emollient; emulsifying agent; plasticizer.

7 Applications in Pharmaceutical Formulation or Technology

Mineral oil and lanolin alcohols is an oily liquid used in topical pharmaceutical formulations and cosmetics as an emulsifying agent with emollient properties; *see* Table I. It is used as a primary emulsifier in the preparation of water-in-oil creams and lotions and as an auxiliary emulsifier and stabilizing agent in oil-in-water creams and lotions.

Table I: Uses of mineral oil and lanolin alcohols.

Use	Concentration (%)
Emollient	3.0–6.0
Emulsifier in w/o creams and lotions	5.0–15.0
Emulsifier in o/w creams and lotions	0.5–6.0

8 Description

A pale yellow-colored, oily liquid with a faint characteristic sterol odor.

9 Pharmacopeial Specifications

—

10 Typical Properties

Acid value: $\leqslant 1$
Arsenic: $\leqslant 2$ ppm
Ash: $\leqslant 0.2\%$
Heavy metals: $\leqslant 20$ ppm
HLB value: ≈ 8
Hydroxyl value: 10–15
Iodine number: $\leqslant 12$
Microbiological count: the total bacterial count, when packaged, is less than 10 per gram of sample.
Moisture content: $\leqslant 0.2\%$
Saponification value: $\leqslant 2$
Solubility: soluble 1 in 2 parts of chloroform, 1 in 4 parts of castor oil, and 1 in 4 parts of corn oil. Practically insoluble in ethanol (95%) and water. Precipitation occurs in hexane.
Specific gravity: 0.840–0.860 at 25°C

11 Stability and Storage Conditions

Mineral oil and lanolin alcohols is stable and should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Lanolin alcohols is incompatible with coal tar, ichthammol, phenol, and resorcinol.

13 Method of Manufacture

Lanolin alcohols is dissolved in mineral oil.

14 Safety

Mineral oil and lanolin alcohols is generally regarded as an essentially nontoxic and nonirritant material. However, lanolin alcohols may be irritant to the skin and causes hypersensitivity in some individuals.(1)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Accepted for use in topical pharmaceutical formulations and cosmetics. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Lanolin alcohols; mineral oil; petrolatum and lanolin alcohols.

18 Comments

See Lanolin Alcohols and Mineral Oil for further information.

19 Specific References

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21 Authors

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22 Date of Revision

11 August 2005.

Monoethanolamine

1 Nonproprietary Names

BP: Ethanolamine
USPNF: Monoethanolamine

2 Synonyms

β-Aminoethyl alcohol; colamine; ethylolamine; β-hydroxyethylamine; 2-hydroxyethylamine.

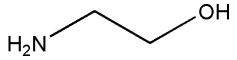
3 Chemical Name and CAS Registry Number

2-Aminoethanol [141-43-5]

4 Empirical Formula and Molecular Weight

C_2H_7NO 61.08

5 Structural Formula



6 Functional Category

Alkalizing agent; emulsifying agent.

7 Applications in Pharmaceutical Formulation or Technology

Monoethanolamine is used primarily in pharmaceutical formulations for buffering purposes and in the preparation of emulsions. Other uses include as a solvent for fats and oils and as a stabilizing agent in an injectable dextrose solution of phenytoin sodium.

Monoethanolamine is also used to produce a variety of salts with therapeutic uses. For example, a salt of monoethanolamine with vitamin C is used for intramuscular injection, while the salicylate and undecenoate monoethanolamine salts are utilized respectively in the treatment of rheumatism and as an antifungal agent. However, the most common therapeutic use of monoethanolamine is in the production of ethanolamine oleate injection, which is used as a sclerosing agent.(1)

8 Description

Monoethanolamine is a clear, colorless or pale yellow-colored, moderately viscous liquid with a mild, ammoniacal odor.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for monoethanolamine.

Test	BP 2004	USPNF 23
Identification	+	—
Characters	+	—
Specific gravity	1.014–1.023	1.013–1.016
Refractive index	1.453–1.459	—
Related substances	⩽2.0%	—
Distilling range	—	167–173°C
Residue on ignition	—	⩽0.1%
Organic volatile impurities	—	+
Assay	98.0–100.5%	98.0–100.5%

10 Typical Properties

Acidity/alkalinity: pH = 12.1 for a 0.1 N aqueous solution.
Boiling point: 170.8°C
Critical temperature: 341°C
Density:
 1.0117 g/cm^3 at 25°C;
 0.9998 g/cm^3 at 40°C;
 0.9844 g/cm^3 at 60°C.
Dissociation constant: $pK_a = 9.4$ at 25°C
Flash point (open cup): 93°C
Hygroscopicity: very hygroscopic.
Melting point: 10.3°C
Refractive index: $n_D^{20} = 1.4539$
Solubility: *see* Table II.

Table II: Solubility of monoethanolamine.

Solvent	Solubility at 20°C
Acetone	Miscible
Benzene	1 in 72
Chloroform	Miscible
Ethanol (95%)	Miscible
Ethyl ether	1 in 48
Glycerol	Miscible
Methanol	Miscible
Water	Miscible

Surface tension: 48.8 mN/m at 20°C
Vapor density (relative): 2.1 (air = 1)
Vapor pressure: 53.3 Pa (0.4 mmHg) at 20°C
Viscosity (dynamic):
 18.95 mPa s (18.95 cP) at 25°C;
 5.03 mPa s (5.03 cP) at 60°C.

11 Stability and Storage Conditions

Monoethanolamine is very hygroscopic and is unstable when exposed to light. Aqueous monoethanolamine solutions may be sterilized by autoclaving.

When monoethanolamine is stored in large quantities, stainless steel is preferable for long-term storage. Copper, copper alloys, zinc, and galvanized iron are corroded by amines and should not be used for construction of storage containers. Ethanolamines readily absorb moisture and carbon dioxide from the air; they also react with carbon dioxide. This can be prevented by sealing the monoethanolamine under an inert gas. Smaller quantities of monoethanolamine should be stored in an airtight container, protected from light, in a cool, dry place.

12 Incompatibilities

Monoethanolamine contains both a hydroxy group and a primary amine group and will thus undergo reactions characteristic of both alcohols and amines. Ethanolamines will react with acids to form salts and esters. Discoloration and precipitation will take place in the presence of salts of heavy metals. Monoethanolamine reacts with acids, acid anhydrides, acid chlorides, and esters to form amide derivatives, and with propylene carbonate or other cyclic carbonates to give the corresponding carbonates.

As a primary amine, monoethanolamine will react with aldehydes and ketones to yield aldimines and ketimines. Additionally, monoethanolamine will react with aluminum, copper, and copper alloys to form complex salts. A violent reaction will occur with acrolein, acrylonitrile, epichlorohydrin, propiolactone, and vinyl acetate.

13 Method of Manufacture

Monoethanolamine is prepared commercially by the ammonolysis of ethylene oxide. The reaction yields a mixture of monoethanolamine, diethanolamine, and triethanolamine, which is separated to obtain the pure products. Monoethanolamine is also produced from the reaction between nitromethane and formaldehyde.

14 Safety

Monoethanolamine is an irritant, caustic material, but when it is used in neutralized parenteral and topical pharmaceutical formulations it is not usually associated with adverse effects, although hypersensitivity reactions have been reported. Monoethanolamine salts are generally regarded as being less toxic than monoethanolamine.

LD_{50} (mouse, IP): 0.05 g/kg⁽²⁾
LD_{50} (mouse, oral): 0.7 g/kg
LD_{50} (rabbit, skin): 1.0 g/kg
LD_{50} (rat, IM): 1.75 g/kg
LD_{50} (rat, IP): 0.07 g/kg
LD_{50} (rat, IV): 0.23 g/kg
LD_{50} (rat, oral): 1.72 g/kg
LD_{50} (rat, SC): 1.5 g/kg

15 Handling Precautions

When handling concentrated solutions of monoethanolamine, personal protective equipment such as an appropriate respirator, chemically resistant gloves, safety goggles, and other protective clothing should be worn. Transfer or prepare monoethanolamine solutions only in a chemical fume hood.

Vapors may flow along surfaces to distant ignition sources and flash back. Closed containers exposed to heat may explode. Contact with strong oxidizers may cause fire.

In the UK, the short-term (15-minute) occupational exposure limit for monoethanolamine is 15 mg/m^3 (6 ppm) and the long-term exposure limit (8-hour TWA) is 7.6 mg/m^3 (3 ppm).(3)

16 Regulatory Status

Included in parenteral and nonparenteral medicines licensed in the UK and US. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Diethanolamine; triethanolamine.

18 Comments

The EINECS number for monoethanolamine is 205-483-3.

19 Specific References

1 Crotty B, Wood LJ, Willett IR, *et al.* The management of acutely bleeding varices by injection sclerotherapy. *Med J Aust* 1986; **145**: 130–133.
2 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 1607–1608.
3 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.

20 General References

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21 Authors

SR Goskonda, JC Lee.

22 Date of Revision

15 August 2005.

Monosodium Glutamate

1 Nonproprietary Names

USPNF: Monosodium glutamate

2 Synonyms

Chinese seasoning; E621; glutamic acid monosodium salt; glutamic acid, sodium salt; MSG; monosodium L-glutamate monohydrate; natrii glutamas; sodium L-glutamate; sodium glutamate monohydrate; sodium hydrogen L-(+)-2-aminoglutarate monohydrate.

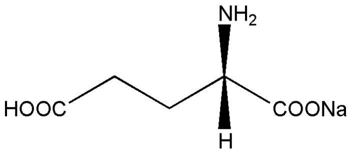
3 Chemical Name and CAS Registry Number

Glutamic acid monosodium salt monohydrate [142-47-2]

4 Empirical Formula and Molecular Weight

$C_5H_8NO_4Na$	169.13 (anhydrous)
$C_5H_8NO_4Na \cdot H_2O$	187.13 (monohydrate)

5 Structural Formula



6 Functional Category

Buffering agent; flavor enhancer.

7 Applications in Pharmaceutical Formulation or Technology

Monosodium glutamate is used in oral pharmaceutical formulations as a buffer and a flavor enhancer. For example, it is used with sugar to improve the palatability of bitter-tasting drugs and can reduce the metallic taste of iron-containing liquids. However, the most widespread use of monosodium glutamate is as a flavor enhancer in food products. Typically, 0.2–0.9% is used in normally salted foods, although products such as soy protein can contain 10–30%. The use of monosodium glutamate in food products has been controversial owing to the relatively high number of adverse reactions attributed to the substance, which gives rise to the so-called 'Chinese Restaurant Syndrome' (*see* Section 18).

8 Description

Monosodium glutamate occurs as white free-flowing crystals or a crystalline powder. It is practically odorless and has a meat-like taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for monosodium glutamate.

Test	USPNF 23
Identification	+
Clarity and color of solution	+
Specific rotation	+24.8° to +25.3°
pH (5% solution)	6.7–7.2
Loss on drying	⩽0.5%
Chloride	⩽0.25%
Lead	⩽10 ppm
Heavy metals	⩽0.002%
Organic volatile impurities	+
Assay	99.0–100.5%

10 Typical Properties

Acidity/alkalinity: pH = 7.0 (0.2% w/v aqueous solution)
Melting point: 232°C
Solubility: soluble in water; sparingly soluble in ethanol (95%).
Specific rotation $[\alpha]_D^{25}$ +24.2° to +25.5° at 25°C (8.0% w/v in 1.0 N HCl)

11 Stability and Storage Conditions

Aqueous solutions of monosodium glutamate may be sterilized by autoclaving. Monosodium glutamate should be stored in a tight container in a cool, dry place.

12 Incompatibilities

—

13 Method of Manufacture

Monosodium glutamate is the monosodium salt of the naturally occurring L-form of glutamic acid. It is commonly manufactured by fermentation of carbohydrate sources such as sugar beet molasses. In general, sugar beet products are used in Europe and the USA. Other carbohydrate sources such as sugar cane and tapioca are used in Asia.

14 Safety

Monosodium glutamate is widely used in foods and oral pharmaceutical formulations. It is generally regarded as moderately toxic on ingestion or intravenous administration. Adverse effects include somnolence, hallucinations and distorted perceptions, headache, dyspnea, nausea or vomiting, and dermatitis. The lowest lethal oral dose in humans is reported to be 43 mg/kg.(1) *See also* Section 18.

LD_{50} (cat, SC): 8.0 g/kg(1)
LD_{50} (guinea pig, IP): 15 g/kg
LD_{50} (mouse, IP): 3.8 g/kg
LD_{50} (mouse, IV): 30 g/kg
LD_{50} (mouse, oral): 11.4 g/kg
LD_{50} (mouse, SC): 8.2 g/kg
LD_{50} (rat, IP): 4.3 g/kg

LD_{50} (rat, IV): 3.3 g/kg
LD_{50} (rat, oral): 16.6 g/kg
LD_{50} (rat, SC): 5.6 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. When heated to decomposition, monosodium glutamate emits toxic fumes of NO_x and Na_2O.

16 Regulatory Status

GRAS listed. Accepted in Europe for use as a food additive in certain applications. Included in the FDA Inactive Ingredients Guide (oral syrup). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

—

18 Comments

Monosodium glutamate has been associated with reports of adverse reactions termed 'Chinese Restaurant Syndrome' after it was first self-reported by a physician who regularly experienced numbness and palpitations after consuming Chinese food.(2)

Subsequent to this first report, numerous other anecdotal reports of adverse reactions to monosodium glutamate were made, with symptoms occurring at doses of 1.5–12 g. Reactions include paresthesias or a skin burning sensation, facial pressure or tightness sensation, and substernal chest pressure. Severity of reaction corresponded with increased dose. Reports of 'Chinese Restaurant Syndrome' in children are rare. A variety of other adverse reactions to monosodium glutamate have also been reported including flushing, asthma,(3) headache, behavioral abnormalities, and ventricular tachycardia.(4)

Placebo-controlled, blinded, trials of monosodium glutamate consumption have, however, largely failed to reproduce the full effects of 'Chinese Restaurant Syndrome' as it was originally described and symptoms may be simply due to dyspepsia. Some dose-dependent adverse reactions may be attributed to monosodium glutamate, with doses of 5 g producing reactions in 30% of individuals tested.(5) In the USA, the FDA has stated that monosodium glutamate and related substances are safe food ingredients for most people when used at 'customary' levels.(6)

Monosodium glutamate monohydrate 32 g is approximately equivalent to anhydrous monosodium glutamate 29 g or glutamic acid 25 g. Each gram of monosodium glutamate monohydrate represents 5.3 mmol (5.3 mEq) of sodium.

A specification for monosodium glutamate is contained in the Food Chemicals Codex (FCC). The EINECS number for monosodium glutamate is 205-538-1.

19 Specific References

1 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 2573.
2 Kwok HM. Chinese restaurant syndrome. *N Engl J Med* 1968; **278**: 796.
3 Allen DH, Baker GH. Chinese restaurant asthma. *N Engl J Med* 1981; **305**: 1154–1155.
4 Smolinske SC. *Handbook of Food, Drug and Cosmetic Excipients*. Boca Raton, FL: CRC Press, 1992: 235–241.
5 Kenney RA. The Chinese restaurant syndrome: an anecdote revisited. *Food Chem Toxicol* 1986; **24**: 351–354.
6 Anonymous. Monosodium glutamate safe for most people, says FDA. *Pharm J* 1996; **256**: 83.

20 General References

Chevassus H, Renard E, Bertrand G, *et al*. Effects of oral monosodium L-glutamate on insulin secretion and glucose tolerance in healthy volunteers. *Br J Clin Pharmacol* 2002; **53**(6): 641–643.
Japan Pharmaceutical Excipients Council. *Japanese Pharmaceutical Excipients Directory 1996*. Tokyo: Yakuji Nippo, 1996: 335.
Walker R. The significance of excursions above the ADI. Case study: monosodium glutamate. *Reg Toxicol Pharmacol* 1999; **30**: S119–S121.

21 Authors

PJ Weller.

22 Date of Revision

14 August 2005.

Monothioglycerol

1 Nonproprietary Names

USPNF: Monothioglycerol

2 Synonyms

1-Mercaptoglycerol; 1-mercapto-2,3-propanediol; monothioglycerin; α-monothioglycerol; thioglycerin; 1-thioglycerol.

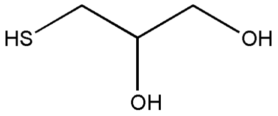
3 Chemical Name and CAS Registry Number

3-Mercapto-1,2-propanediol [96-27-5]

4 Empirical Formula and Molecular Weight

$C_3H_8O_2S$ 108.16

5 Structural Formula



6 Functional Category

Antimicrobial preservative; antioxidant.

7 Applications in Pharmaceutical Formulation or Technology

Monothioglycerol is used as an antioxidant in pharmaceutical formulations, mainly in parenteral preparations.(1) Monothioglycerol is reported to have some antimicrobial activity.(2–4) It is also widely used in cosmetic formulations such as depilating agents.

Therapeutically, monothioglycerol has been used in a 0.02% w/w aqueous solution to stimulate wound healing, and as a 0.1% w/w jelly in atrophic rhinitis.

8 Description

Monothioglycerol occurs as a colorless or pale-yellow colored, viscous, hygroscopic liquid with a slight odor of sulfide.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for monothioglycerol.

Test	USPNF 23
Specific gravity	1.241–1.250
Refractive index	1.521–1.526
pH (10% aqueous solution)	3.5–7.0
Water	⩽5.0%
Residue on ignition	⩽0.1%
Selenium	⩽0.003%
Heavy metals	⩽0.002%
Organic volatile impurities	+
Assay (anhydrous basis)	97.0–101.0%

10 Typical Properties

Acidity/alkalinity: pH = 3.5–7.0 (10% w/v aqueous solution)
Boiling point: 118°C
Flash point: 110°C
Refractive index: n_D^{25} = 1.521–1.526
Solubility: miscible with ethanol (95%); freely soluble in water; practically insoluble in ether.
Specific gravity: 1.241–1.250

11 Stability and Storage Conditions

Monothioglycerol is unstable in alkaline solutions. Monothioglycerol should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Monothioglycerol can react with oxidizing materials.

13 Method of Manufacture

Monothioglycerol is prepared by heating an ethanolic solution of 3-chloro-1,2-propanediol with potassium bisulfide.

14 Safety

Monothioglycerol is generally regarded as a relatively nontoxic and nonirritant material at the concentrations used as a pharmaceutical excipient. It is used in topical and injectable preparations.

Undiluted monothioglycerol is considered a poison by the IP and IV routes; it has also been reported to be mutagenic.(5)

LD_{50} (cat, IV): 0.22 g/kg(5)
LD_{50} (mouse, IP): 0.34 g/kg
LD_{50} (rabbit, IV): 0.25 g/kg
LD_{50} (rat, IP): 0.39 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Monothioglycerol is flammable when exposed to heat or flame; when heated to decomposition it emits toxic fumes of SO_x.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IM, IV and other injections). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

—

18 Comments

The EINECS number for monothioglycerol is 202-495-0.

19 Specific References

1 Kasraian K, Kuzniar AA, Wilson GG, Wood JA. Developing an injectable formula containing an oxygen sensitive drug: case study of danofloxacin injectable. *Pharm Dev Technol* 1999; **4**(4): 475–480.
2 Jensen KK, Javor GT. Inhibition of *Escherichia coli* by thioglycerol. *Antimicrob Agents Chemother* 1981; **19**: 556–561.
3 Javor GT. Depression of adenoslymethionine content of *Escherichia coli* by thioglycerol. *Antimicrob Agents Chemother* 1983; **24**: 860–867.
4 Javor GT. Inhibition of respiration of *Escherichia coli* by thioglycerol. *Antimicrob Agents Chemother* 1983; **24**: 868–870.
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20 General References

Nealon DA, Pettit SM, Henderson AR. Diluent pH and the stability of the thiol group in monothioglycerol, *N*-acetyl-L-cysteine, and 2-mercaptoethanol. *Clin Chem* 1981; **27**(3): 505–506.

21 Authors

PJ Sheskey, PJ Weller.

22 Date of Revision

14 August 2005.

Myristic Acid

1 Nonproprietary Names

None adopted.

2 Synonyms

Edenor C14 98-100; *n*-tetradecanoic acid; 1-tridecanecarboxylic acid.

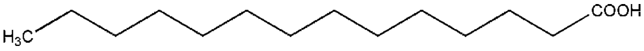
3 Chemical Name and CAS Registry Number

Tetradecanoic acid [544-63-8]

4 Empirical Formula and Molecular Weight

$C_{14}H_{28}O_2$ 228.37

5 Structural Formula



6 Functional Category

Emulsifying agent; skin penetrant; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Myristic acid is used in oral and topical pharmaceutical formulations. Myristic acid has been evaluated as a penetration enhancer in melatonin transdermal patches in rats(1) and bupropion formulations on human cadaver skin.(2) Further studies have assessed the suitability of myristic acid in oxymorphone formulations(3) and clobetasol 17-propionate topical applications.(4)

8 Description

Myristic acid occurs as an oily white crystalline solid with a faint odor.

9 Pharmacopeial Specifications

See Section 18.

10 Typical Properties

Boiling point: 326.2°C
Flash point: >110°C
Melting point: 54.5°C
Solubility: soluble in acetone, benzene, chloroform, ethanol (95%), ether, and aromatic and chlorinated solvents; practically insoluble in water.
Specific gravity: 0.860–0.870

11 Stability and Storage Conditions

The bulk material should be stored in a well-closed container in a cool, dry, place.

12 Incompatibilities

Myristic acid is incompatible with strong oxidizing agents and bases.

13 Method of Manufacture

Myristic acid occurs naturally in nutmeg butter and in most animal and vegetables fats. Synthetically, it may be prepared by electrolysis of methyl hydrogen adipate and decanoic acid or by Maurer oxidation of myristyl alcohol.

14 Safety

Myristic acid is used in oral and topical pharmaceutical formulations and is generally regarded as nontoxic and nonirritant at the levels employed as an excipient. However, myristic acid is reported to be an eye and skin irritant at high levels and is poisonous by intravenous administration. Mutation data have also been reported.(5)

LD_{50} (mouse, IV): 43 mg/kg(5)
LD_{50} (rat, oral): >10 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled. Acrid smoke and irritating fumes are emitted when myristic acid is heated to decomposition.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral capsules). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Lauric acid; myristyl alcohol; palmitic acid; potassium myristate; sodium myristate; stearic acid.

Myristyl alcohol

Empirical formula: $C_{14}H_{30}O$
Molecular weight: 214.39
CAS number: [112-72-1]
Melting point: 37–39°C
Boiling point: 277–288°C
Specific gravity: 0.8
Solubility: practically insoluble in water.

Potassium myristate

Empirical formula: $C_{14}H_{28}O_2K$
Molecular weight: 267.52
CAS number: [13429-27-1]

Comments: potassium myristate is used as surfactant and emulsifying agent in pharmaceutical formulations. The EINECS number for potassium myristate is 236-550-5.

Sodium myristate

Empirical formula: $C_{14}H_{28}O_2Na$
Molecular weight: 251.41
CAS number: [822-12-8]
Comments: sodium myristate is used as an emulsifying agent in pharmaceutical formulations. The EINECS number for sodium myristate is 212-487-9.

18 Comments

Although not included in any pharmacopeias, a specification for myristic acid is contained in the Food Chemicals Codex (FCC) and in the Japanese Pharmaceutical Excipients (JPE), *see* Table I.

The EINECS number for myristic acid is 208-875-2.

Table I: Food Chemicals Codex(6) and Japanese Pharmaceutical Excipients(7) specifications for myristic acid.

Test	FCC 1996	JPE 2004
Identification	—	+
Acid value	242–249	240–250
Heavy metals	⩽10 mg/kg	+
Iodine value	⩽1.0	⩽1.0
Residue on ignition	⩽0.1%	⩽0.1%
Saponification value	242–251	—
Melting point	48–55.5°C	—
Unsaponifiable matter	⩽1%	—
Water	⩽0.2%	—
Ester value	—	⩽3

19 Specific References

1 Kanikkannan N, Andega S, Burton S, *et al*. Formulation and *in vitro* evaluation of transdermal patches of melatonin. *Drug Dev Ind Pharm* 2004; **30**: 205–212.

2 Gondaliya D, Pundarikakshudu K. Studies in formulation and pharmacotechnical evaluation of controlled release transdermal delivery system of bupropion. *AAPS PharmSci Tech* 2003; **4**: E3.

3 Aungst BJ, Blake JA, Rogers NJ, Hussain MA. Transdermal oxymorphone formulation development and methods for evaluating flux and lag times for two skin permeation-enhancing vehicles. *J Pharm Sci* 1990; **79**: 1072–1076.

4 Fang JY, Shen KL, Huang YB, *et al*. Evaluation of topical application of clobetasol 17-propionate from various cream bases. *Drug Dev Ind Pharm* 1999; **25**: 7–14.

5 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 2586.

6 *Food Chemicals Codex*, 4th edn. Washington, DC: National Academy Press, 1996: 262.

7 Japan Pharmaceutical Excipients Council. *Japanese Pharmaceutical Excipients 2004*. Tokyo: Yakuji Nippo, 2004: 572.

20 General References

—

21 Authors

LY Galichet.

22 Date of Revision

24 May 2005.

Neohesperidin Dihydrochalcone

1 Nonproprietary Names

BP: Neohesperidin dihydrochalcone
PhEur: Neohesperidin dihydrochalconum

2 Synonyms

Citrosa; 3,5-dihydroxy-4-(3-hydroxy-4-methoxyhydrocinnamoyl)phenyl-2-O-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranoside; 3,5-dihydroxy-4-[3-(3-hydroxy-4-methoxyphenyl)propionyl]phenyl-2-O-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranoside; E959; neohesperidin DC; neohesperidin DHC; neohesperidine dihydrochalcone; NHDC; 1-propanone, 1-[4-[[2-O-6-deoxy-α-L-mannopyranosyl)-β-D-glycopyranosyl]oxy]-2,6-dihydroxyphenyl]-3-(3-hydroxy-4-methoxyphenyl); *Sukor.*

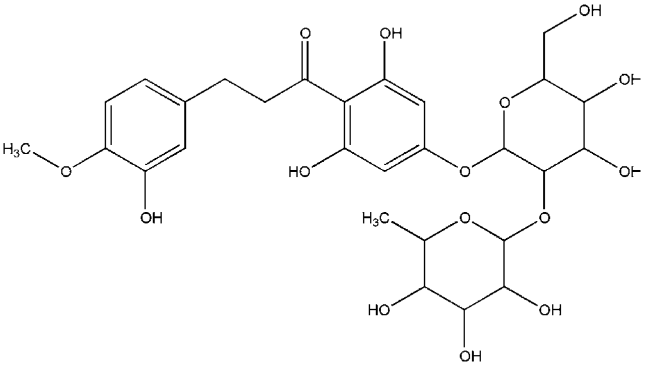
3 Chemical Name and CAS Registry Number

1-[4-[[2-O-(6-Deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-2,6-dihydroxyphenyl]-3-(3-hydroxy-4-methoxyphenyl)propan-1-one [20702-77-6]

4 Empirical Formula and Molecular Weight

$C_{28}H_{36}O_{15}$ 612.58

5 Structural Formula



6 Functional Category

Flavor enhancer; sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

Neohesperidin dihydrochalcone is a synthetic intense sweetening agent approximately 1500–1800 times sweeter than sucrose and 20 times sweeter than saccharin. Structurally it is an analogue of neohesperidin, a flavanone that occurs naturally in Seville oranges (*Citrus aurantium*). Neohesperidin dihydrochalcone is used in pharmaceutical and food applications as a sweetening agent and flavor enhancer. The sweetness profile is characterized by a lingering sweet/menthol-like aftertaste.(1) The typical level used in foods is 1–5 ppm although much higher levels may be used in certain applications such as chewing gum. Synergistic effects occur with other intense and bulk sweeteners such as acesulfame K, aspartame, polyols, and saccharin.(2)

In pharmaceutical applications, neohesperidin dihydrochalcone is useful in masking the unpleasant bitter taste of a number of drugs such as antacids, antibiotics, and vitamins. In antacid preparations levels of 10–30 ppm result in improved palatability.

8 Description

Neohesperidin dihydrochalcone occurs as a white or yellowish-white powder with an intensely sweet taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for neohesperidin dihydrochalcone.

Test	PhEur 2005
Identification	+
Characters	+
Appearance of solution	+
Related substances	+
Heavy metals	⩽10 ppm
Water	⩽12.0%
Sulfated ash	⩽0.2%
Assay (anhydrous substance)	96.0–101.0%

10 Typical Properties

Hygroscopicity: slightly hygroscopic; absorbs up to 15% of water.
Melting point: 156–158°C
Solubility: *see* Table II.

Table II: Solubility of neohesperidin dihydrochalcone.

Solvent	Solubility at 25°C unless otherwise stated
Dichloromethane	Practically insoluble
Dimethyl sulfoxide	Freely soluble
Methanol	Soluble
Water	1 in 2000 at 22°C 1 in 1.54 at 80°C

11 Stability and Storage Conditions

Neohesperidin dihydrochalcone is stable for over three years when stored at room temperature.(1)

Accelerated stability studies on aqueous solutions stored at 30–60°C and pH 1–7 for 140 days indicate that neohesperidin dihydrochalcone solutions are likely to be stable for 12 months at room temperature and pH 2–6.(3) Solutions formulated with some or all of the water replaced by solvents with a lower dielectric constant are reported to have longer shelf-lives.(4)

The bulk material should be stored in a cool, dry, place protected from light.

12 Incompatibilities

—

13 Method of Manufacture

Neohesperidin dihydrochalcone is synthesized commercially from either of the bitter-flavanones neohesperidin or naringin by catalytic hydrogenation under alkaline conditions in a process first described in the 1960s, in which neohesperidin is purified by recrystallization from water solutions.(5) Neohesperidin dihydrochalcone is obtained by the alkaline hydrogenation of neohesperidin.(6)

14 Safety

Neohesperidin dihydrochalcone is accepted for use in food products either as a sweetener or flavor modifier in a number of areas including Europe, US, Australia, New Zealand, and several countries in Africa and Asia. It is also used in a number of oral pharmaceutical formulations.

Animal toxicity studies suggest that neohesperidin dihydrochalcone is a nontoxic, nonteratogenic, and noncarcinogenic material at the levels used in foods and pharmaceuticals.(7,8) In Europe, an acceptable daily intake of 0–5 mg/kg bodyweight has been established.(9,10)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe.

17 Related Substances

Hesperidin.

Hesperidin

Empirical formula: $C_{28}H_{34}O_{15}$
Molecular weight: 610.56
CAS number: [520-26-3]
Synonyms: (2S)-7-[[6-O-(6-Deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-2,3-dihydro-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-4*H*-1-benzopyran-4-one; hesperitin 7-rhamnoglucoside; hesperetin-7-rutinoside.
Melting point: 258–262°C
Solubility: freely soluble in diluted alkalis and pyridines; soluble in formamide; slightly soluble in methanol and hot glacial acetic acid.
Comments: hesperedin is the predominant flavonoid in lemons and sweet oranges (*Citrus sinensis*).

18 Comments

Neohesperidin dihydrochalcone is sufficiently soluble in aqueous solutions for most pharmaceutical and food applications; however, solubility may be improved by dissolving in ethanol, glycerin, propylene glycol, or aqueous mixtures of these solvents.(10) Solubility may also be improved by mixing with other intense or bulk sweeteners.(2)

Neohesperidin dihydrochalcone in weak concentrations has been shown not to enhance the taste of aqueous sucrose solutions.(6)

The EINECS number for neohesperidin dihydrochalcone is 243-978-6.

19 Specific References

1 Cano J, Montijano H, Lopez Cremades F. Masking the bitter taste of pharmaceuticals. *Manuf Chem* 2000; **71**(7): 16–17.
2 Benavente-Garcia O, Castillo J, Del Bano MJ, Lorente J. Improved water solubility of neohesperidin dihydrochalcone sweetener blends. *J Agric Food Chem* 2001; **49**(1): 189–191.
3 Canales I, Borrego F, Lindley MG. Neohesperidin dihydrochalcone stability in aqueous buffer solutions. *J Food Sci* 1993; **58**: 589–591, 643.
4 Montijano H, Borrego F. Hydrolysis of the intense sweetener neohesperidine dihydrochalcone in water–organic solvent mixtures. *Int J Food Sci Technol* 1999; **34**: 291–294.
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8 Waalkens-Berendsen DH, Kuilman-Wahls ME, Bar A. Embryotoxicity and teratogenicity study with neohesperidin dihydrochalcone in rats. *Regul Toxicol Pharmacol* 2004; **40**(1): 74–79.
9 Horowitz RM, Gentili B. Dihydrochalcone sweeteners from citrus flavanones. In: O'Brien Nabors L, Gelardi RC, eds. *Alternative Sweeteners*, 2nd edn. New York: Marcel Dekker, 1991: 97–115.
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21 Authors

PJ Weller.

22 Date of Revision

23 May 2005.

Nitrogen

1 Nonproprietary Names

BP: Nitrogen
JP: Nitrogen
PhEur: Nitrogenium
USPNF: Nitrogen

2 Synonyms

Azote; E941.

3 Chemical Name and CAS Registry Number

Nitrogen [7727-37-9]

4 Empirical Formula and Molecular Weight

N_2 28.01

5 Structural Formula

N_2

6 Functional Category

Aerosol propellant; air displacement.

7 Applications in Pharmaceutical Formulation or Technology

Nitrogen and other compressed gases such as carbon dioxide and nitrous oxide are used as propellants for topical pharmaceutical aerosols. They are also used in other aerosol products that work satisfactorily with the coarse aerosol spray produced with compressed gases, e.g. furniture polish and window cleaner. Nitrogen is insoluble in water and other solvents, and therefore remains separated from the actual pharmaceutical formulation.

Advantages of compressed gases as aerosol propellants are that they are inexpensive; of low toxicity; and practically odorless and tasteless. In contrast to liquefied gases, their pressures change relatively little with temperature. However, there is no reservoir of propellant in the aerosol and as a result the pressure decreases as the product is used, changing the spray characteristics.

Misuse of a product by the consumer, such as using a product inverted, results in the discharge of the vapor phase instead of the liquid phase. Most of the propellant is contained in the vapor phase and therefore some of the propellant will be lost and the spray characteristics will be altered. Additionally, the sprays produced using compressed gases are very wet. However, recent developments in valve technology have reduced the risk of misuse by making available valves which will spray only the product (not propellant) regardless of the position of the container. Additionally, barrier systems will also prevent loss of propellant.

Nitrogen is also used to displace air from solutions subject to oxidation, by sparging, and to replace air in the headspace above products in their final packaging, e.g. in parenteral products packaged in glass ampoules. Nitrogen is also used for the same purpose in many food products.

8 Description

Nitrogen occurs naturally as approximately 78% v/v of the atmosphere. It is a nonreactive, noncombustible, colorless, tasteless, and odorless gas. It is usually handled as a compressed gas, stored in metal cylinders.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for nitrogen.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Odor	—	—	+
Carbon monoxide	—	⩽5 ppm	⩽0.001%
Carbon dioxide	+	⩽300 ppm	—
Water	—	⩽67 ppm	—
Oxygen	—	⩽50 ppm	⩽1.0%
Assay	⩾99.5%	⩾99.5%	⩾99.0%

10 Typical Properties

Boiling point: −195.8°C
Critical pressure: 3.39 mPa (33.49 atm)
Critical temperature: −147.2°C
Density: 0.967 g/cm^3 for vapor at 21°C.
Flammability: nonflammable
Melting point: −210°C
Solubility: practically insoluble in water and most solvents; soluble in water under pressure.
Vapor density (absolute): 1.25 g/cm^3 at standard temperature and pressure.
Vapor density (relative): 0.97 (air = 1)

11 Stability and Storage Conditions

Nitrogen is stable and chemically unreactive. It should be stored in tightly sealed metal cylinders in a cool, dry place.

12 Incompatibilities

Generally compatible with most materials encountered in pharmaceutical formulations and food products.

13 Method of Manufacture

Nitrogen is obtained commercially, in large quantities, by the fractional distillation of liquefied air.

14 Safety

Nitrogen is generally regarded as a nontoxic and nonirritant material. However, it is an asphyxiant and inhalation of large quantities is therefore hazardous. *See also* Section 18.

15 Handling Precautions

Handle in accordance with procedures for handling metal cylinders containing liquefied or compressed gases. Eye protection, gloves, and protective clothing are recommended. Nitrogen is an asphyxiant and should be handled in a well-ventilated environment. The oxygen content of air in the working environment should be monitored and should not be permitted to fall below 19% v/v at normal atmospheric pressure.(1)

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (injections; dental preparations; nasal sprays; oral solutions; rectal gels). Accepted for use as a food additive in Europe. Included in parenteral and nonparenteral medicines licensed in the UK and USA. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Carbon dioxide; nitrous oxide.

18 Comments

Different grades of nitrogen are commercially available that have, for example, especially low moisture levels.

Nitrogen is commonly used as a component of the gas mixtures breathed by divers. Under high pressure, such as when diving at great depths, nitrogen will dissolve in blood and lipid. If decompression is too rapid, decompression sickness may occur when the nitrogen effervesces from body stores to form gas emboli.

A specification for nitrogen is contained in the Food Chemicals Codex (FCC). The EINECS number for nitrogen is 231-783-9.

19 Specific References

1 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.

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21 Authors

CJ Sciarra, JJ Sciarra.

22 Date of Revision

23 August 2005.

Nitrous Oxide

1 Nonproprietary Names

BP: Nitrous oxide
JP: Nitrous oxide
PhEur: Dinitrogenii oxidum
USP: Nitrous oxide

2 Synonyms

Dinitrogen monoxide; E942; laughing gas; nitrogen monoxide.

3 Chemical Name and CAS Registry Number

Dinitrogen oxide [10024-97-2]

4 Empirical Formula and Molecular Weight

N_2O 44.01

5 Structural Formula

N_2O

6 Functional Category

Aerosol propellant; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Nitrous oxide and other compressed gases such as carbon dioxide and nitrogen are used as propellants for topical pharmaceutical aerosols. They are also used in other aerosol products that work satisfactorily with the coarse aerosol spray that is produced with compressed gases, e.g. furniture polish and window cleaner.

The advantages of compressed gases as aerosol propellants are that they are inexpensive, of low toxicity, and practically odorless and tasteless. In contrast to liquefied gases, their pressures change relatively little with temperature. However, there is no reservoir of propellant in the aerosol, and as a result the pressure decreases as the product is used, changing the spray characteristics.

Misuse of a product by the consumer, such as using a product inverted, results in the discharge of the vapor phase instead of the liquid phase. Since most of the propellant is contained in the vapor phase, some of the propellant will be lost and the spray characteristics will be altered. Additionally, the sprays produced using compressed gases are very wet. However, recent developments in valve technology have reduced the risk of misuse by making available valves which will spray only the product (not propellant) regardless of the position of the container. Additionally, barrier systems will also prevent loss of propellant.

Therapeutically, nitrous oxide is best known as an anesthetic administered by inhalation. When used as an anesthetic it has strong analgesic properties but produces little muscle relaxation. Nitrous oxide is always administered in conjunction with oxygen since on its own it is hypoxic.

8 Description

Nitrous oxide is a nonflammable, colorless and odorless, sweet-tasting gas. It is usually handled as a compressed gas, stored in metal cylinders.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for nitrous oxide.

Test	JP 2001	PhEur 2005	USP 28
Production	–	+	–
Identification	+	+	+
Characters	–	+	–
Acidity or alkalinity	+	–	–
Carbon dioxide	+	⩽300 ppm	⩽0.03%
Carbon monoxide	+	⩽5 ppm	⩽0.001%
Nitric oxide	–	–	⩽1 ppm
Nitrogen dioxide	–	–	⩽1 ppm
Nitric monoxide and nitrogen dioxide	–	⩽2 ppm	–
Halogens	–	–	⩽1 ppm
Oxidizing substances	+	–	–
Potassium permanganate-reducing substances	+	–	–
Ammonia	–	–	⩽0.0025%
Chloride	+	–	–
Air	–	–	⩽1.0%
Water	–	⩽67 ppm	<0.03%
Assay	⩾97.0%	⩾98.0%	⩾99.0%

10 Typical Properties

Boiling point: −88.5°C
Critical pressure: 7.27 mPa (71.7 atm)
Critical temperature: 36.5°C
Density: 1.53 g/cm^3
Flammability: nonflammable, but supports combustion.
Freezing point: −90.8°C
Solubility: freely soluble in chloroform, ethanol (95%), ether, and oils; soluble 1 in 1.5 volumes of water at 20°C and 101.3 kPa pressure.
Vapor density (absolute): 1.97 g/cm^3 at standard temperature and pressure.
Vapor density (relative): 1.52 (air = 1)

11 Stability and Storage Conditions

Nitrous oxide is essentially nonreactive and stable except at high temperatures; at a temperature greater than 500°C nitrous oxide decomposes to nitrogen and oxygen. Explosive mixtures may be formed with other gases such as ammonia, hydrogen, and other fuels. Nitrous oxide should be stored in a tightly sealed metal cylinder in a cool, dry place.

12 Incompatibilities

Nitrous oxide is generally compatible with most materials encountered in pharmaceutical formulations, although it may react as a mild oxidizing agent.

13 Method of Manufacture

Nitrous oxide is prepared by heating ammonium nitrate to about 170°C. This reaction also forms water.

14 Safety

Nitrous oxide is most commonly used therapeutically as an anesthetic and analgesic. Reports of adverse reactions to nitrous oxide therefore generally concern its therapeutic use, where relatively large quantities of the gas may be inhaled, rather than its use as an excipient.

The main complications associated with nitrous oxide inhalation occur as a result of hypoxia. Prolonged administration may also be harmful. Nitrous oxide is rapidly absorbed on inhalation.

15 Handling Precautions

Handle in accordance with procedures for handling metal cylinders containing liquefied or compressed gases. Eye protection, gloves, and protective clothing are recommended. Nitrous oxide is an anesthetic gas and should be handled in a well-ventilated environment. In the UK, the recommended long-term (8-hour TWA) occupational exposure limit for nitrous oxide is 183 mg/m^3 (100 ppm).(1)

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in nonparenteral medicines licensed in the UK and USA. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Carbon dioxide; nitrogen.

18 Comments

A mixture of 50% nitrous oxide and 50% oxygen (*Entonox*, BOC) is commonly used as an analgesic administered by inhalation.

A specification for nitrous oxide is contained in the Food Chemicals Codex (FCC). The EINECS number for nitrous oxide is 233-032-0.

19 Specific References

1 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.

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21 Authors

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22 Date of Revision

23 August 2005.

Octyldodecanol

1 Nonproprietary Names

PhEur: Octyldodecanolum
USPNF: Octyldodecanol

2 Synonyms

Eutanol G PH; isoarachidyl alcohol; isoeicosyl alcohol; *Jarcol 1-20*; *Jeecol ODD*; octildodecanol; 2-octyldecyl alcohol; 2-octyl-1-dodecanol.

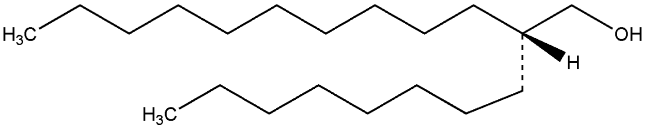
3 Chemical Name and CAS Registry Number

Octyldodecanol [5333-42-6]

4 Empirical Formula and Molecular Weight

$C_{20}H_{42}O$ 298.62

5 Structural Formula



6 Functional Category

Emollient; emulsifying agent; lubricant; solvent; thickening agent.

7 Applications in Pharmaceutical Formulation or Technology

Octyldodecanol is widely used in cosmetics and pharmaceutical applications as an emulsifying and opacifying agent. It is primarily used in topical applications because of its lubricating and emollient properties.

Octyldodecanol has been used in the preparation of oil/water microemulsions investigated as the vehicle for the dermal administration of drugs having no or low skin penetration.(1) Octyldodecanol has also been evaluated as a solvent for naproxen when applied topically.(2)

8 Description

Octyldodecanol occurs as a clear, colorless, or yellowish, oily liquid.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for octyldodecanol.

Test	PhEur 2005	USPNF 23
Characters	+	—
Identification	+	+
Acidity or alkalinity	+	—
Relative density	≈ 0.840	—
Refractive index	≈ 1.455	—
Optical rotation	$-0.10°$ to $+10°$	—
Hydroxyl value	175–190	175–190
Iodine value	$\leqslant 8$	$\leqslant 8$
Saponification value	$\leqslant 5$	$\leqslant 5$
Acid value	—	$\leqslant 0.5$
Peroxide value	$\leqslant 0.5$	—
Heavy metals	$\leqslant 10$ ppm	—
Water	$\leqslant 0.5\%$	—
Sulfated ash	$\leqslant 0.1\%$	—
Organic volatile impurities	—	+
Assay	$>90.0\%$	$>90.0\%$

10 Typical Properties

Flash point: 180°C–200°C
Melting point: < -20°C
Refractive index: $n_D^{20} = 1.45$–1.46
Solubility: miscible with ethanol (95%); practically insoluble in water.
Specific gravity: 0.83–0.85 at 20°C
Viscosity (dynamic): 58–64 mPa s (58–64 cP) at 20°C

11 Stability and Storage Conditions

The bulk material should be stored in a well-closed container in a cool, dry, place protected from light. In the original unopened container, octyldodecanol can be stored for two years protected from moisture at below 30°C.

12 Incompatibilities

Octyldodecanol is generally compatible with most materials encountered in cosmetic and pharmaceutical formulations.

13 Method of Manufacture

Octyldodecanol is produced by the condensation of two molecules of decyl alcohol. It also occurs naturally in small quantities in plants.

14 Safety

Octyldodecanol is widely used in cosmetics and topical pharmaceutical formulations and is generally regarded as nontoxic and nonirritant at the levels employed as an excipient.

In acute oral toxicity studies in rats fed 5 g/kg of undiluted octyldodecanol, no deaths were observed.(3) In an acute dermal toxicity study, intact and abraded skin sites of guinea pigs were treated with 3 g/kg of undiluted octyldodecanol under occlusive patches; no deaths occurred and no gross skin lesions were observed.(3) Octyldodecanol caused either no ocular irritation or minimal, transient irritation in the eyes of rabbits.(3) However, some sources describe undiluted octyldodecanol as an eye and severe skin irritant.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. When heated to decomposition, octyldodecanol emits acrid smoke and irritating fumes.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (topical, transdermal, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

—

18 Comments

A specification for octyldodecanol is included in Japanese Pharmaceutical Excipients (JPE).(4)

The EINECS number for octyldodecanol is 226-242-9.

19 Specific References

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21 Authors

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22 Date of Revision

22 August 2005.

Oleic Acid

1 Nonproprietary Names

BP: Oleic acid
PhEur: Acidum oleicum
USPNF: Oleic acid

2 Synonyms

Crodolene; *Crossential 094*; elaic acid; *Emersol*; *Glycon*; *Groco*; *Hy-Phi*; *Industrene*; *Metaupon*; *Neo-Fat*; *cis*-9-octadecenoic acid; 9,10-octadecenoic acid; oleinic acid; *Priolene*.

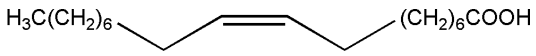
3 Chemical Name and CAS Registry Number

(*Z*)-9-Octadecenoic acid [112-80-1]

4 Empirical Formula and Molecular Weight

$C_{18}H_{34}O_2$ 282.47

5 Structural Formula



6 Functional Category

Emulsifying agent; skin penetrant.

7 Applications in Pharmaceutical Formulation or Technology

Oleic acid is used as an emulsifying agent in foods and topical pharmaceutical formulations. It has also been used as a penetration enhancer in transdermal formulations,(1–14) to improve the bioavailability of poorly water-soluble drugs in tablet formulations,(15) and as part of a vehicle in soft gelatin capsules.

Oleic acid has been reported to act as an ileal 'break' that slows down the transit of luminal contents through the distal portion of the small bowel.(16)

Oleic acid labeled with ^{131}I and ^{3}H is used in medical imaging.

8 Description

A yellowish to pale brown, oily liquid with a characteristic lard-like odor and taste.

Oleic acid consists chiefly of (*Z*)-9-octadecenoic acid together with varying amounts of saturated and other unsaturated acids. It may contain a suitable antioxidant.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for oleic acid.

Test	PhEur 2005	USPNF 23
Identification	+	—
Characters	+	—
Specific gravity	≈0.892	0.889–0.895
Residue on ignition	—	⩽1 mg
Total ash	⩽0.1%	—
Mineral acids	—	+
Neutral fat or mineral oil	—	+
Fatty acid composition	+	—
Myristic acid	⩽5.0%	—
Palmitic acid	⩽16.0%	—
Palmitoleic acid	⩽8.0%	—
Stearic acid	⩽6.0%	—
Oleic acid	65.0–88.0%	—
Linoleic acid	⩽18.0%	—
Linolenic acid	⩽4.0%	—
Fatty acids of chain length greater than C_{18}	⩽4.0%	—
Acid value	195–204	196–204
Iodine value	89–105	85–95
Peroxide value	⩽10.0	—
Congealing temperature	—	+
From animal sources	—	3–10°C
From vegetable sources	—	10–16°C
Margaric acid	—	—
From animal sources	⩽4.0%	—
From vegetable sources	⩽0.2%	—
Color of solution	+	—
Organic volatile impurities	—	+
Assay	65–88%	—

10 Typical Properties

Acidity/alkalinity: pH = 4.4 (saturated aqueous solution)
Autoignition temperature: 363°C
Boiling point: 286°C at 13.3 kPa (100 mmHg) (decomposition at 80–100°C)
Density: 0.895 g/cm^3
Flash point: 189°C
Melting point: 4°C
Refractive index: n_D^{26} = 1.4585
Solubility: miscible with benzene, chloroform, ethanol (95%), ether, hexane, and fixed and volatile oils; practically insoluble in water.
Vapor pressure: 133 Pa (1 mmHg) at 176.5°C
Viscosity (dynamic): 26 mPa s (26 cP) at 25°C

11 Stability and Storage Conditions

On exposure to air, oleic acid gradually absorbs oxygen, darkens in color, and develops a more pronounced odor. At atmospheric pressure, it decomposes when heated at 80–100°C.

Oleic acid should be stored in a well-filled, well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

Incompatible with aluminum, calcium, heavy metals, iodine solutions, perchloric acid, and oxidizing agents. Oleic acid reacts with alkalis to form soaps.

13 Method of Manufacture

Oleic acid is obtained by the hydrolysis of various animal and vegetable fats or oils, such as olive oil, followed by separation of the liquid acids. It consists chiefly of (*Z*)-9-octadecenoic acid. Oleic acid that is to be used systemically should be prepared from edible sources.

14 Safety

Oleic acid is used in oral and topical pharmaceutical formulations.

In vitro tests have shown that oleic acid causes rupture of red blood cells (hemolysis), and intravenous injection or ingestion of a large quantity of oleic acid can therefore be harmful. The effects of oleic acid on alveolar(17) and buccal(18) epithelial cells *in vitro* have also been studied; the *in vitro* and *in vivo* effects of oleic acid on rat skin have been reported.(19) Oleic acid is a moderate skin irritant; it should not be used in eye preparations.

An acceptable daily intake for the calcium, sodium, and potassium salts of oleic acid was not specified by the WHO since the total daily intake of these materials in foods was such that they did not pose a hazard to health.(20)

LD_{50} (mouse, IV): 0.23 g/kg(21)
LD_{50} (rat, IV): 2.4 mg/kg
LD_{50} (rat, oral): 74 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Gloves and eye protection are recommended.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (inhalation and nasal aerosols, tablets, topical and transdermal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Ethyl oleate.

18 Comments

Several grades of oleic acid are commercially available ranging in color from pale yellow to reddish brown. Different grades become turbid at varying temperatures depending upon the amount of saturated acid present. Usually, oleic acid contains 7–12% saturated acids, such as stearic and palmitic acid, together with other unsaturated acids, such as linoleic acid. A specification for oleic acid is contained in the Food Chemicals Codex (FCC). The EINECS number for oleic acid is 204-007-1.

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12 Bhatia KS, Gao S, Singh J. Effect of penetration enhancers and iontophoresis on the FT-IR spectroscopy and LHRH permeability through porcine skin. *J Control Release* 1997; **47**: 81–89.
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15 Tokumura T, Tsushima Y, Tatsuishi K, *et al.* Enhancement of the oral bioavailability of cinnarizine in oleic acid in beagle dogs. *J Pharm Sci* 1987; **76**: 286–288.
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20 General References

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21 Authors

CG Cable.

22 Date of Revision

23 August 2005.

Oleyl Alcohol

1 Nonproprietary Names

PhEur: Alcohol oleicus
USP: Oleyl alcohol

2 Synonyms

HD-Eutanol V PH; *Ocenol*; *cis*-9-octadecen-1-ol; oleic alcohol; oleo alcohol; oleol.

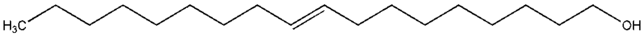
3 Chemical Name and CAS Registry Number

(*Z*)-9-Octadecen-1-ol [143-28-2]

4 Empirical Formula and Molecular Weight

$C_{18}H_{36}O$ 268.48

5 Structural Formula



6 Functional Category

Antifoaming agent; dissolution enhancer; emollient; emulsifying agent; skin penetrant; sustained-release agent.

7 Applications in Pharmaceutical Formulation or Technology

Oleyl alcohol is mainly used in topical pharmaceutical formulations and has been used in transdermal delivery formulations.(1–6) It has been utilized in the development of biodegradable injectable thermoplastic oligomers,(7) and in aerosol formulations of insulin(8) and albuterol.(9)

Therapeutically, it has been suggested that oleyl alcohol may exhibit antitumor properties via transmembrane permeation.(10)

8 Description

Oleyl alcohol occurs as a pale yellow oily liquid that gives off acrid fumes when heated.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for oleyl alcohol.

Test	PhEur 2005	USPNF 23
Appearance	+	—
Cloud point	$<10°C$	$<10°C$
Refractive index	1.458–1.460	1.458–1.460
Acid value	$\leqslant 1$	$\leqslant 1$
Hydroxyl value	205–215	205–215
Iodine value	—	85–95
Saponification value	$\leqslant 2$	—
Composition of fatty alcohols	+	—

10 Typical Properties

Boiling point: 182–184°C at 1.5 atm
Density: 0.850 g/cm^3 at 20°C
Flash point: 170°C
Melting point: 13–19°C
Partition coefficient: log P (octanol/water) = 7.50.
Refractive index: n_D^{25} = 1.4582
Solubility: soluble in ethanol (95%), and ether; practically insoluble in water.

11 Stability and Storage Conditions

The bulk material should be stored in a well-closed container in a cool, dry, place.

12 Incompatibilities

—

13 Method of Manufacture

Oleyl alcohol occurs naturally in fish oils. Synthetically, it can be prepared from butyl oleate by a Bouveault–Blanc reduction with sodium and butyl alcohol. An alternative method of manufacture is by the hydrogenation of triolein in the presence of zinc chromite.

14 Safety

Oleyl alcohol is mainly used in topical pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material at the levels employed as an excipient. However, contact dermatitis due to oleyl alcohol has been reported.(11)

The results of acute oral toxicity and percutaneous studies in animals with products containing 8% oleyl alcohol indicate a very low toxicity.(12) Formulations containing 8% or 20% oleyl alcohol administered by gastric intubation, at doses up to 10 g/kg body weight, caused no deaths and no toxic effects in rats.(12)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (topical emulsions and ointments). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Oleic acid; oleyl oleate.

Oleyl oleate

Empirical formula: $C_{36}H_{68}O_2$
Molecular weight: 532.9
CAS number: [3687-45-4]
Refractive index: n_D^{25} = 1.464–1.468
Specific gravity: 0.860–0.884
Solubility: miscible with chloroform and with diethyl ether; slightly soluble in ethanol.

18 Comments

A specification for oleyl alcohol is included in the Japanese Pharmaceutical Excipients (JPE) 2004.(13) The EINECS number for oleyl alcohol is 205-597-3.

19 Specific References

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Murota K, Kawada T, Matsui N, *et al*. Oleyl alcohol inhibits intestinal long-chain fatty acid absorption in rats. *J Nutr Sci Vitaminol (Tokyo)* 2000; **46**: 302–308.

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21 Authors

LY Galichet.

22 Date of Revision

17 August 2005.

Olive Oil

1 Nonproprietary Names

BP: Refined olive oil
JP: Olive oil
PhEur: Olivae oleum raffinatum
USPNF: Olive oil

2 Synonyms

Gomenoleo oil; pure olive oil; olea europaea oil; oleum olivae.

3 Chemical Name and CAS Registry Number

Olive oil [8001-25-00]

4 Empirical Formula and Molecular Weight

Olive oil is a mixture of fatty acid glycerides. Analysis of olive oil shows a high proportion of unsaturated fatty acids, and a typical analysis shows that the composition of the fatty acids is as follows:

Myristic acid (14 : 0), $\leqslant$0.5%
Palmitic acid (16 : 0), 7.5–20.0%
Palmitoleic acid (16 : 1), 0.3–5.0%
Hepatodecenoic acid (17 : 1), $\leqslant$0.3%
Stearic acid (18 : 0), 0.5–5.0%
Oleic acid (18 : 1), 55.0–83.0%
Linoleic acid (18 : 2), 3.5–21.0%
Linoleic acid (18 : 3), $\leqslant$0.9%
Arachidic acid (20 : 0), $\leqslant$0.6%
Eicosaenoic acid (20 : 1), $\leqslant$0.4%
Behenic acid (22:0), $\leqslant$0.2%
Lignoceric acid (24:0), $\leqslant$1.0%
Sterols are also present.

5 Structural Formula

See Section 4.

6 Functional Category

Oleaginous vehicle.

7 Applications in Pharmaceutical Formulation or Technology

Olive oil has been used in enemas, liniments, ointments, plasters, and soap. It has also been used in oral capsules and solutions, and as a vehicle for oily injections.

It has been used in topically applied lipogels of methyl nicotinate.(1) It has also been used to soften ear wax.(2) Olive oil has been used in combination with soybean oil to prepare lipid emulsion for use in pre-term infants.(3)

Olive oil is used widely in the food industry as a cooking oil and for preparing salad dressings. In cosmetics, olive oil is used as a solvent, and also as a skin and hair conditioner. Types of products containing olive oil include shampoos and hair conditioners, cleansing products, topical creams and lotions, and sun-tan products.

8 Description

Olive oil is the fixed oil from the fruit of *Olea europaea*. It occurs as a clear, colorless or greenish-yellow, oily liquid.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Flash point: 225°C
Refractive index: n_D^{25} = 1.4657–1.4893
Smoke point: 160–188°C
Solubility: slightly soluble in ethanol (95%); miscible with ether, chloroform, light petroleum (50–70°C), and carbon disulfide.

11 Stability and Storage Conditions

When cooled, olive oil becomes cloudy at approximately 10°C, and becomes a butterlike mass at 0°C.

Olive oil should be stored in a cool, dry place in a tight, well-filled container, protected from light.

For refined oil intended for use in the manufacture of parenteral dosage forms, the PhEur 2005 requires that the bulk oil be stored under an inert gas.

12 Incompatibilities

Olive oil may be saponified by alkali hydroxides. As it contains a high proportion of unsaturated fatty acids, olive oil is prone to oxidation and is incompatible with oxidizing agents.

13 Method of Manufacture

Virgin olive oil is produced by crushing olives (the fruit of *Olea europaea*), typically using an edge runner mill. The oil is then expressed from the crushed mass solely by mechanical or other physical methods under conditions that do not cause deterioration of the oil. Any further treatment that the oil undergoes is limited to washing, decantation, centrifugation, and filtration.

Refined olive oil is obtained from virgin olive oil by refining methods that do not alter the initial glyceride content of the oil.

14 Safety

Olive oil is used widely as an edible oil and in food preparations and products such as cooking oils and salad dressings. It is used in cosmetics and topical pharmaceutical formulations. Olive oil is generally regarded as a relatively nonirritant and nontoxic material when used as an excipient.

Olive oil is a demulcent and has mild laxative properties when taken orally. It has been used in topical formulations as an emollient and to sooth inflamed skin; to soften the skin and crusts in eczema; in massage oils; and to soften earwax.(2)

There have been isolated reports that olive oil may cause a reaction in hypersensitive individuals. However, these incidences are relatively uncommon.(4–6) Olive oil is an infrequent

Table I: Pharmacoepeial specifications for olive oil.

Test	JP 2001	PhEur 2005(a)	USPNF 23
Identification	—	+	—
Characters	+	+	—
Acid value	⩽1.0	⩽0.5	—
Peroxide value	—	⩽5.0	—
Saponification value	186–194	—	190–195
Unsaponifiable matter	⩽1.5%	⩽1.5%	—
Iodine value	79–88	—	79–88
Specific gravity	—	—	0.910–0.915
Free fatty acids	—	—	+
Alkaline impurities	—	+	—
Absorbance at 270 nm	—	0.20–1.20	—
Composition of fatty acids	—	+	—
Saturated fatty acids of chain length less than C_{16}	—	⩽0.1%	—
Palmitic acid	—	7.5–20.0%	—
Palmitoleic acid	—	⩽3.5%	—
Stearic acid	—	0.5–5.0%	—
Oleic acid	—	56.0–85.0%	—
Linoleic acid	—	3.5–20.0%	—
Linoleic acid (equivalent chain length on polyethylene-glycol adipate 19.7)	—	⩽1.2%	—
Arachidic acid	—	⩽0.7%	—
Eicosenoic acid	—	⩽0.4%	—
Behenic acid	—	⩽0.2%	—
Lignoceric acid	—	⩽0.2%	—
Sterols	—	+	—
β-Sitostanol, Δ^5,24-stigmastadienol, clerosterol, sitostanol, Δ^5-avenasterol, and Δ^5,23-stigmastadienol	—	⩾93.0%	—
Cholesterol	—	⩽0.5%	—
Δ^7-stigmasterol	—	⩽0.5%	—
Campesterol	—	⩽4.0%	—
Stigmasterol	—	Not more than that of	
campesterol	—		
Sesame oil	—	+	+
Water	—	+	—
Cottonseed oil	—	—	+
Drying oil	+	—	—
Peanut oil	+	—	+
Teaseed oil	—	—	+
Heavy metals	—	—	⩽0.001%
Organic volatile impurities	—	—	+
Solidification range of fatty acids	—	—	17–26°C

(a) The PhEur 2005 material refers to refined olive oil.

sensitizer and does not appear to be a significant allergen in the USA, possibly due to the development of oral tolerance.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Olive oil spills are slippery and an inert oil absorbent should be used to cover the oil, which can then be disposed of according to the appropriate legal regulations.

16 Regulatory Status

Olive oil is an edible oil. Included in the FDA Inactive Ingredients Guide (oral capsules and solution; topical solutions). Included in nonparenteral medicines licensed in Europe. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Crude olive-pomace oil; extra virgin olive oil; fine virgin olive oil; lampante virgin olive oil; olive-pomace oil; refined olive-pomace oil; virgin olive oil.

Crude olive-pomace oil

Comments: crude olive-pomace oil is olive-pomace oil that is intended for refining prior to its use in food for human consumption, or that is intended for technical purposes.

Extra virgin olive oil

Comments: extra virgin oil is a virgin oil that has an organoleptic rating of not less than 6.5, and a free acidity (as oleic acid) of not more than 1.0 g per 100 g.

Fine virgin olive oil

Comments: fine virgin oil has an organoleptic rating of not less than 5.5, and a free acidity (as oleic acid) of not more than 1.5 g per 100 g.

Lampante virgin olive oil

Comments: lampante virgin olive oil is virgin olive oil that is not fit for consumption unless it is further processed. This grade of oil is intended for refining or technical purposes.

Olive-pomace oil

Comments: olive-pomace oil is the oil obtained from the solvent extraction of olive pomace, but does not include oils obtained by reesterification processes or any mixture with oils of any kind. Olive-pomace oil of commerce is a blend of refined olive-pomace oil and virgin olive oil that is fit for human consumption. *See also* Section 18.

Refined olive-pomace oil

Comments: refined olive-pomace oil is obtained from crude olive-pomace oil by refining methods that do not alter the initial glyceride structure. It is intended for consumption, or blended with virgin olive oil.

Virgin olive oil

Comments: virgin olive oil has an organoleptic rating of not less than 3.5, and a free acidity (as oleic acid) of not more than 3.3 g per 100 g. The PhEur 2005 contains a monograph on virgin olive oil as well as refined olive oil.

18 Comments

Olive oil is available in a variety of different grades; *see* Section 17. All olive oils are graded according to the degree of acidity.

The flavor, color, and fragrance of olive oils may vary, depending on the region where the olives are grown, the condition of the crops, and the type of olive used.

Olive-pomace oil is obtained from the olive pomace by solvent extraction. The use of solvent extraction causes small changes in the typical fatty acid composition of the oil, and changes in organoleptic properties and impurities. Other oils can be prepared by reesterification of the appropriate combination of fatty acids with glycerol. Olive-pomace oils or reesterified oils cannot be called olive oil.

19 Specific References

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20 General References

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21 Authors

RC Moreton.

22 Date of Revision

31 August 2005.

Palmitic Acid

1 Nonproprietary Names

BP: Palmitic acid
PhEur: Acidum palmiticum

2 Synonyms

Cetylic acid; *Edenor C16 98-100*; *Emersol 140*; *Emersol 143*; *n*-hexadecoic acid; hexadecylic acid; *Hydrofol*; *Hystrene 9016*; *Industrene 4516*; 1-pentadecanecarboxylic acid.

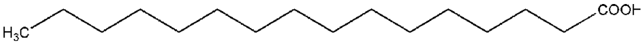
3 Chemical Name and CAS Registry Number

Hexadecanoic acid [57-10-3]

4 Empirical Formula and Molecular Weight

$C_{16}H_{32}O_2$ 256.42

5 Structural Formula



6 Functional Category

Emulsifying agent; skin penetrant; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Palmitic acid is used in oral and topical pharmaceutical formulations. Palmitic acid has been used in implants for sustained release of insulin in rats.(1,2)

8 Description

Palmitic acid occurs as white crystalline scales with a slight characteristic odor and taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for palmitic acid.

Test	PhEur 2005
Appearance	+
Acidity	+
Freezing point	60–66°C
Iodine value	<1
Stearic acid	<6%
Nickel	<1 ppm
Assay	>92.9%

10 Typical Properties

Boiling point: 271.5°C at 100 mmHg
Flash point: >110°C
Melting point: 63–64°C
Solubility: soluble in ethanol (95%); practically insoluble in water.
Specific gravity: 0.849–0.851.

11 Stability and Storage Conditions

The bulk material should be stored in a well-closed container in a cool, dry, place.

12 Incompatibilities

Palmitic acid is incompatible with strong oxidizing agents and bases.

13 Method of Manufacture

Palmitic acid occurs naturally in all animal fats as the glyceride, palmitin, and in palm oil partly as the glyceride and partly uncombined. Palmitic acid is most conveniently obtained from olive oil after removal of oleic acid, or from Japanese beeswax. Synthetically, palmitic acid may be prepared by heating cetyl alcohol with soda lime to 270°C or by fusing oleic acid with potassium hydrate.

14 Safety

Palmitic acid is used in oral and topical pharmaceutical formulations and is generally regarded as nontoxic and nonirritant at the levels employed as an excipient. However, palmitic acid is reported to be an eye and skin irritant at high levels and is poisonous by intravenous administration.

LD_{50} (mouse, IV): 57 mg/kg(3)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. When palmitic acid is heated to decomposition, carbon dioxide and carbon monoxide are formed.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Lauric acid; myristic acid; palmitin; sodium palmitate; stearic acid.

Palmitin

Empirical formula: $C_{51}H_{98}O_6$
Molecular weight: 807.29
CAS number: [555-44-2]
Refractive index: $n_D^{25} = 1.4381$

Specific gravity: 0.886

Solubility: soluble in benzene, chloroform, and ether; practically insoluble in ethanol (95%) and in water.

Sodium palmitate

Synonyms: hexadecanoic acid sodium salt; palmitic acid sodium salt; sodium hexadecanoate.

Empirical formula: $C_{16}H_{31}O_2Na$

Molecular weight: 278.47

CAS number: [408-35-5]

Melting point: 283–290°C

Comments: sodium palmitate is used as a surfactant and emulsifying agent in pharmaceutical formulations. The EINECS number for sodium palmitate is 206-988-1.

18 Comments

A specification for palmitic acid is included in the Food Chemicals Codex(4) and in the Japanese Pharmaceutical Excipients 2004 (JPE).(5) The EINECS number for palmitic acid is 200-312-9.

19 Specific References

1 Wang PY. Palmitic acid as an excipient in implants for sustained release of insulin. *Biomaterials* 1991; **12**: 57–62.

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21 Authors

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22 Date of Revision

17 August 2005.

Paraffin

1 Nonproprietary Names

BP: Hard paraffin
JP: Paraffin
PhEur: Paraffinum solidum
USPNF: Paraffin

2 Synonyms

Hard wax; paraffinum durum; paraffin wax.

3 Chemical Name and CAS Registry Number

Paraffin [8002-74-2]

4 Empirical Formula and Molecular Weight

Paraffin is a purified mixture of solid saturated hydrocarbons having the general formula C_nH_{2n+2}, and is obtained from petroleum or shale oil.

5 Structural Formula

See Section 4.

6 Functional Category

Ointment base; stiffening agent.

7 Applications in Pharmaceutical Formulation or Technology

Paraffin is mainly used in topical pharmaceutical formulations as a component of creams and ointments. In ointments, it may be used to increase the melting point of a formulation or to add stiffness. Paraffin is additionally used as a coating agent for capsules and tablets, and is used in some food applications. Paraffin coatings can also be used to affect the release of drug from ion-exchange resin beads.(1)

8 Description

Paraffin is an odorless and tasteless, translucent, colorless, or white solid. It feels slightly greasy to the touch and may show a brittle fracture. Microscopically, it is a mixture of bundles of microcrystals. Paraffin burns with a luminous, sooty flame. When melted, paraffin is essentially without fluorescence in daylight; a slight odor may be apparent.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for paraffin.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Congealing range	50–75°C	—	47–65°C
Reaction	—	—	+
Heavy metals	$\leqslant$10 ppm	—	—
Arsenic	$\leqslant$2 ppm	—	—
Sulfates	+	+	—
Polycyclic aromatic hydrocarbons	—	+	—
Readily carbonizable substances	+	—	+
Acidity or alkalinity	+	+	—

10 Typical Properties

Density: ≈0.84–0.89 g/cm^3 at 20°C

Melting point: various grades with different specified melting ranges are commercially available.

Solubility: soluble in chloroform, ether, volatile oils, and most warm fixed oils; slightly soluble in ethanol; practically insoluble in acetone, ethanol (95%), and water. Paraffin can be mixed with most waxes if melted and cooled.

11 Stability and Storage Conditions

Paraffin is stable, although repeated melting and congealing may alter its physical properties. Paraffin should be stored at a temperature not exceeding 40°C in a well-closed container.

12 Incompatibilities

—

13 Method of Manufacture

Paraffin is manufactured by the distillation of crude petroleum or shale oil, followed by purification by acid treatment and filtration. Paraffins with different properties may be produced by controlling the distillation and subsequent congealing conditions.

Synthetic paraffin, synthesized from carbon monoxide and hydrogen is also available; *see* Section 17.

14 Safety

Paraffin is generally regarded as an essentially nontoxic and nonirritant material when used in topical ointments and as a coating agent for tablets and capsules. However, granulomatous reactions (paraffinomas) may occur following injection of paraffin into tissue for cosmetic purposes or to relieve pain. Long-term inhalation of aerosolized paraffin may lead to interstitial pulmonary disease. Ingestion of a substantial amount of white soft paraffin has led to intestinal obstruction in one instance.(2–6)

See also Mineral Oil for further information.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. In the UK, the recommended occupational exposure limits for paraffin wax fumes are 2 mg/m^3 long-term (8-hour TWA) and 6 mg/m^3 short-term.(7)

16 Regulatory Status

Accepted in the UK for use in certain food applications. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets, topical emulsions, and ointments). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Light mineral oil; microcrystalline wax; petrolatum; synthetic paraffin.

Synthetic paraffin

Molecular weight: 400–1400

Appearance: a hard, odorless, white wax consisting of a mixture of mostly long-chain, unbranched, saturated hydrocarbons along with a small amount of branched hydrocarbons.

Melting point: 96–105°C

Viscosity (dynamic): 5–15 mPa s (5–15 cP) at 135°C.

Comments: the USPNF 23 states that synthetic paraffin is synthesized by the Fischer–Tropsch process from carbon monoxide and hydrogen, which are catalytically converted to a mixture of paraffin hydrocarbons. The lower molecular weight fractions are removed by distillation and the residue is hydrogenated and further treated by percolation through activated charcoal. This mixture may be fractionated into its components by a solvent-separation method. Synthetic paraffin may contain not more than 0.005% w/w of a suitable antioxidant.

18 Comments

The more highly purified waxes are used in preference to paraffin in many applications because of their specifically controlled physical properties such as hardness, malleability, and melting range. A specification for synthetic paraffin is contained in the Food Chemicals Codex (FCC). The EINECS numbers for paraffin are 232-315-6 and 265-154-5.

19 Specific References

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AH Kibbe.

22 Date of Revision

17 August 2005.

Peanut Oil

1 Nonproprietary Names

BP: Arachis oil
JP: Peanut oil
PhEur: Arachidis oleum raffinatum
USPNF: Peanut oil

2 Synonyms

Aextreff CT; earthnut oil; groundnut oil; katchung oil; nut oil.

3 Chemical Name and CAS Registry Number

Peanut oil [8002-03-7]

4 Empirical Formula and Molecular Weight

A typical analysis of refined peanut oil indicates the composition of the acids present as glycerides to be: arachidic acid 2.4%; behenic acid 3.1%; palmitic acid 8.3%; stearic acid 3.1%; lignoceric acid 1.1%; linoleic acid 26.0%, and oleic acid 56.0%.(1)

5 Structural Formula

See Section 4.

6 Functional Category

Oleaginous vehicle; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Peanut oil is used as an excipient in pharmaceutical formulations primarily as a solvent for sustained-release intramuscular injections. It is also used as a vehicle for topical preparations and as a solvent for vitamins and hormones. In addition, it has been part of sustained-release bead formulations,(2) nasal drug delivery systems,(3) and controlled-release injectables.(4)

Therapeutically, emulsions containing peanut oil have been used in nutrition regimens, in enemas as a fecal softener, and in otic drops to soften ear wax. It is also administered orally, usually with sorbitol, as a gall bladder evacuant prior to cholecystography.

Peanut oil is also widely used as an edible oil.

8 Description

Peanut oil is a colorless or pale yellow-colored liquid that has a faint nutty odor and a bland, nutty taste. At about 3°C it becomes cloudy, and at lower temperatures it partially solidifies.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for peanut oil.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Solidification range	22–33°C	~2°C	26–33°C
Acid value	⩽0.2	⩽0.5	—
Peroxide value	—	⩽5.0	—
Unsaponifiable matter	⩽1.5%	⩽1.0%	⩽1.5%
Specific gravity	0.909–0.916	0.915	0.912–0.920
Alkaline impurities	—	+	—
Cottonseed oil	—	—	+
Rancidity	—	—	+
Iodine value	84–103	—	84–100
Saponification value	188–196	—	185–195
Refractive index at 40°C	—	—	1.462–4.464
Heavy metals	—	—	⩽0.001%
Organic volatile impurities	—	—	+
Water	—	⩽0.3%	—
Composition of fatty acids	—	+	—
Saturated fatty acids $\leqslant C_{14}$	—	⩽0.4%	—
Palmitic acid	—	7.0–16.0%	—
Stearic acid	—	1.3–6.5%	—
Oleic acid	—	35.0–72.0%	—
Linoleic acid	—	13.0–43.0%	—
Linolenic acid	—	⩽0.6%	—
Lignoceric acid	—	0.5–3.0%	—
Arachidic acid	—	0.5–3.0%	—
Eicosenoic acid	—	⩽0.5–2.1%	—
Behenic acid	—	1.0–5.0%	—
Erucic acid	—	⩽0.5%	—

10 Typical Properties

Autoignition temperature: 443°C
Density: 0.915 g/cm^3 at 25°C
Flash point: 283°C
Freezing point: −5°C
Hydroxyl value: 2.5–9.5
Interfacial tension: 19.9 mN/m at 25°C(5)
Refractive index: n_D^{25} = 1.466–1.470
Solubility: very slightly soluble in ethanol (95%); soluble in benzene, carbon tetrachloride, and oils; miscible with carbon disulfide, chloroform, ether, and hexane.
Surface tension: 37.5 mN/m at 25°C(5)
Viscosity (dynamic): 35.2 mPa s (35.2 cP) at 37°C(5)
Viscosity (kinematic): 39.0 mm^2/s (39.0 cSt) at 37°C(5)

11 Stability and Storage Conditions

Peanut oil is an essentially stable material.(6) However on exposure to air it can slowly thicken and may become rancid. Solidified peanut oil should be completely melted and mixed before use. Peanut oil may be sterilized by aseptic filtration or by dry heat, for example, by maintaining it at 150°C for 1 hour.(7)

Peanut oil should be stored in a well-filled, airtight, light-resistant container, at a temperature not exceeding 40°C. Material intended for use in parenteral dosage forms should be stored in a glass container.

12 Incompatibilities

Peanut oil may be saponified by alkali hydroxides.

13 Method of Manufacture

Refined peanut oil is obtained from the seeds of *Arachis hypogaea* Linné (Fam. Leguminosae). The seeds are separated from the peanut shells and are expressed in a powerful hydraulic press. The crude oil has a light yellow to light brown color, and is then purified to make it suitable for food or pharmaceutical purposes. A suitable antioxidant may be added.

14 Safety

Peanut oil is mildly laxative at a dosage of 15–60 mL orally or of 100–500 mL rectally as an enema.

Adverse reactions to peanut oil in foods and pharmaceutical formulations have been reported extensively.(8–18) These include severe allergic skin rashes(8,9) and anaphylactic shock following consumption of peanut butter.(10) Some workers have suggested that the use in infancy of preparations containing peanut oil, including infant formula and topical preparations, is associated with sensitization to peanut, with a subsequent risk of hypersensitivity reactions, and that such products should therefore be avoided or banned.(8–12) However, the role of pharmaceutical preparations in later development of hypersensitivity is disputed since such preparations contain highly refined peanut oil that should not contain the proteins associated with allergic reactions in susceptible individuals.(13–15)

Peanut oil is harmful if administered intravenously and it should not be used in such formulations.(16)

See also Section 18.

15 Handling Precautions

Observe normal handling precautions appropriate to the circumstances and quantity of material handled. Spillages of peanut oil are slippery and should be covered with an inert absorbent material prior to disposal.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IM injections, topical preparations, oral capsules, and vaginal emulsions). Included in parenteral and nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Almond oil; canola oil; corn oil; cottonseed oil; sesame oil; soybean oil; sunflower oil.

18 Comments

As a result of the potentially fatal reactions noted in Section 14, certain food products are now commonly labeled with a statement that they contain peanut oil. A specification for unhydrogenated peanut oil is contained in the Food Chemicals Codex (FCC).

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22 Date of Revision

17 August 2005.

Pectin

1 Nonproprietary Names

USP: Pectin

2 Synonyms

Citrus pectin; E440; methopectin; methyl pectin; methyl pectinate; mexpectin; pectina; pectinic acid.

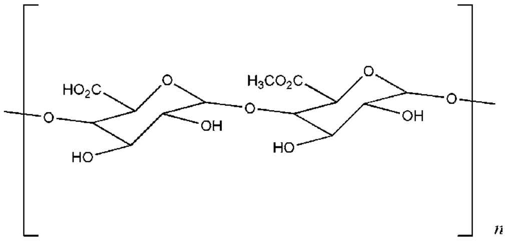
3 Chemical Name and CAS Registry Number

Pectin [9000-65-5]

4 Empirical Formula and Molecular Weight

Pectin is a high-molecular-weight, carbohydrate-like plant constituent consisting primarily of chains of galacturonic acid units linked as 1,4-α-glucosides, with a molecular weight of 30 000–100 000.

5 Structural Formula



Pectin is a complex polysaccharide comprising mainly esterified D-galacturonic acid residues in an α-(1–4) chain. The acid groups along the chain are largely esterified with methoxy groups in the natural product. The hydroxyl groups may also be acetylated.

Pectin gelation characteristics can be divided into two types: high-methoxy and low-methoxy gelation, and sometimes the low-methoxy pectins may contain amine groups. Gelation of high-methoxy pectin usually occurs at pH <3.5. Low-methoxy pectin is gelled with calcium ions and is not dependent on the presence of acid or high solids content. Amidation may interfere with gelation, causing the process to be delayed. However, gels from amidated pectins have the ability to re-heal after shearing.(1)

The USP 28 describes pectin as a purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace. It consists chiefly of partially methoxylated polygalacturonic acids.

6 Functional Category

Adsorbent; emulsifying agent; gelling agent; thickening agent; stabilizing agent.

7 Applications in Pharmaceutical Formulation or Technology

Pectin has been used as an adsorbent and bulk-forming agent, and is present in multi-ingredient preparations for the management of diarrhea, constipation, and obesity;(2) it has also been used as an emulsion stabilizer.(3)

Experimentally, pectin has been used in gel formulations for the oral sustained delivery of ambroxol.(4) Pectin gel beads have been shown to be an effective medium for controlling the release of a drug within the gastrointestinal (GI) tract.(5) It has also been used in a colon-biodegradable pectin matrix with a pH-sensitive polymeric coating, which retards the onset of drug release, overcoming the problems of pectin solubility in the upper GI tract.(6–9) Amidated pectin matrix patches have been investigated for the transdermal delivery of chloroquine,(10) and gelling pectin formulations for the oral sustained delivery of paracetamol have been investigated *in situ*.(11) Pectin-based matrices with varying degrees of esterification have been evaluated as oral controlled-release tablets. Low-methoxy pectins were shown to have a release rate more sensitive to the calcium content of the formulation.(12) Pectins have been used as a component in the preparation of mixed polymer microsphere systems with the intention of producing controlled drug release.(13)

8 Description

Pectin occurs as a coarse or fine, yellowish-white, odorless powder that has a mucilaginous taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for pectin.

Test	USP 28
Identification	+
Loss on drying	⩽10.0%
Arsenic	⩽3 ppm
Lead	⩽5 μg/g
Sugars and organic acids	+
Microbial limits	+
Assay	
Methoxy groups	⩽6.7%
Galacturonic acid	⩽74.0%

10 Typical Properties

Acidity/alkalinity: pH = 6.0–7.2

Solubility: soluble in water; insoluble in ethanol (95%) and other organic solvents.

11 Stability and Storage Conditions

Pectin is a nonreactive and stable material; it should be stored in a cool, dry place.

12 Incompatibilities

—

13 Method of Manufacture

Pectin is obtained from the diluted acid extract from the inner portion of the rind of citrus fruits or from apple pomace.

14 Safety

Pectin is used in oral pharmaceutical formulations and food products and is generally regarded as an essentially nontoxic and nonirritant material.

Low toxicity by the subcutaneous route has been reported.(14)

LD$_{50}$ (mouse, SC): 6.4 g/kg(14)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. When pectin is heated to decomposition, acrid smoke and irritating fumes are emitted.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (dental paste; oral powders; topical pastes). Included in the Canadian List of Acceptable Non-medicinal Ingredients. Included in nonparenteral medicines licensed in the UK.

17 Related Substances

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18 Comments

Pectin has been used in film-coating formulations containing chitosan and hydroxypropylmethyl cellulose in the investigation of the biphasic drug-release properties of film-coated paracetamol tablets, both *in vitro*,(15,16) and *in vivo*.(17) It has been shown that chitosan acts as a crosslinking agent for concentrated pectin solutions.(18)

Pectin gel systems have been used to show the partition and release of aroma compounds in foods during storage.(19)

A specification for pectin is included in the Food Chemical Codex (FCC). In the food industry it is used as an emulsifying agent, gelling agent, thickener, and stabilizer. Cosmetically, it is used as a binder, emulsifying agent and viscosity-controlling agent.

The EINECS number for pectin is 232-553-0.

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22 Date of Revision

26 August 2005.

Petrolatum

1 Nonproprietary Names

BP: Yellow soft paraffin
JP: Yellow petrolatum
PhEur: Vaselinum flavum
USP: Petrolatum

2 Synonyms

Merkur; mineral jelly; petroleum jelly; *Silkolene*; *Snow white*; *Soft white*; yellow petrolatum; yellow petroleum jelly.

3 Chemical Name and CAS Registry Number

Petrolatum [8009-03-8]

4 Empirical Formula and Molecular Weight

Petrolatum is a purified mixture of semisolid saturated hydrocarbons having the general formula C_nH_{2n+2}, and is obtained from petroleum. The hydrocarbons consist mainly of branched and unbranched chains although some cyclic alkanes and aromatic molecules with paraffin side chains may also be present. The USP 28 and PhEur 2005 material may contain a suitable stabilizer (antioxidant) that must be stated on the label. The inclusion of a stabilizer is not discussed in the JP 2001 monograph.

5 Structural Formula

See Section 4.

6 Functional Category

Emollient; ointment base.

7 Applications in Pharmaceutical Formulation or Technology

Petrolatum is mainly used in topical pharmaceutical formulations as an emollient-ointment base; it is poorly absorbed by the skin. Petrolatum is also used in creams and transdermal formulations and as an ingredient in lubricant formulations for medicated confectionery together with mineral oil.

Therapeutically, sterile gauze dressings containing petrolatum may be used for nonadherent wound dressings or as a packing material.(1) Petrolatum is additionally widely used in cosmetics and in some food applications. *See* Table I.

Table I: Uses of petrolatum.

Use	Concentration (%)
Emollient topical creams	10–30
Topical emulsions	4–25
Topical ointments	Up to 100

8 Description

Petrolatum is a pale yellow to yellow-colored, translucent, soft unctuous mass. It is odorless, tasteless, and not more than slightly fluorescent by daylight, even when melted.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for petrolatum.

Test	JP 2001	PhEur 2005	USP 28
Characters	—	+	—
Specific gravity at 60°C	—	—	0.815–0.880
Melting range	38–60°C	—	38–60°C
Drop point	—	40–60°C	—
Consistency	—	100–300	100–300
Alkalinity	+	+	+
Acidity	+	+	+
Residue on ignition	⩽0.05%	—	⩽0.1%
Sulfated ash	—	⩽0.05%	—
Organic acids	+	—	+
Polycyclic aromatic hydrocarbons	—	+	—
Fixed oils, fats and resins	+	—	+
Color	+	—	+
Light absorption	—	+	—
Heavy metals	⩽30 ppm	—	—
Arsenic	⩽2 ppm	—	—
Sulfur compounds	+	—	—

10 Typical Properties

Refractive index: n_D^{60} = 1.460–1.474

Solubility: practically insoluble in acetone, ethanol, hot or cold ethanol (95%), glycerin, and water; soluble in benzene, carbon disulfide, chloroform, ether, hexane, and most fixed and volatile oils.

Viscosity (dynamic): the rheological properties of petrolatum are determined by the ratio of the unbranched chains to the branched chains and cyclic components of the mixture. Petrolatum contains relatively high amounts of branched and cyclic hydrocarbons, in contrast to paraffin, which accounts for its softer character and makes it an ideal ointment base.(2–5)

11 Stability and Storage Conditions

Petrolatum is an inherently stable material owing to the unreactive nature of its hydrocarbon components; most stability problems occur because of the presence of small quantities of impurities. On exposure to light, these impurities may be oxidized to discolor the petrolatum and produce an undesirable odor. The extent of the oxidation varies depending upon the source of the petrolatum and the degree of refinement. Oxidation may be inhibited by the inclusion of a suitable antioxidant such as butylated hydroxyanisole, butylated hydroxytoluene, or alpha tocopherol.

Petrolatum should not be heated for extended periods above the temperature necessary to achieve complete fluidity (approximately 70°C). *See also* Section 18.

Petrolatum may be sterilized by dry heat. Although petrolatum may also be sterilized by gamma irradiation, this process affects the physical properties of the petrolatum such as swelling, discoloration, odor, and rheological behavior.(6,7)

Petrolatum should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

Petrolatum is an inert material with few incompatibilities.

13 Method of Manufacture

Petrolatum is manufactured from the semisolid residue that remains after the steam or vacuum distillation of petroleum.(8) This residue is dewaxed and/or blended with stock from other sources, along with lighter fractions, to give a product with the desired consistency. Final purification is performed by a combination of high-pressure hydrogenation or sulfuric acid treatment followed by filtration through adsorbents. A suitable antioxidant may be added.

14 Safety

Petrolatum is mainly used in topical pharmaceutical formulations and is generally considered to be a nonirritant and nontoxic material.

Animal studies, in mice, have shown petrolatum to be nontoxic and noncarcinogenic following administration of a single subcutaneous 100 mg dose. Similarly, no adverse effects were observed in a 2-year feeding study with rats fed a diet containing 5% of petrolatum blends.(9)

Although petrolatum is generally nonirritant in humans following topical application, rare instances of allergic hypersensitivity reactions have been reported,(10–12) as have cases of acne, in susceptible individuals following repeated use on facial skin.(13) However, given the widespread use of petrolatum in topical products, there are few reports of irritant reactions. The allergic components of petrolatum appear to be polycyclic aromatic hydrocarbons present as impurities. The quantities of these materials found in petrolatum vary depending upon the source and degree of refining. Hypersensitivity appears to occur less with white petrolatum and it is therefore the preferred material for use in cosmetics and pharmaceuticals.

Petrolatum has also been tentatively implicated in the formation of spherulosis of the upper respiratory tract following use of a petrolatum-based ointment packing after surgery,(14) and lipoid pneumonia following excessive use in the perinasal area.(15) Other adverse reactions to petrolatum include granulomas (paraffinomas) following injection into soft tissue.(16) Also, when taken orally, petrolatum acts as a mild laxative and may inhibit the absorption of lipids and lipid-soluble nutrients.

Petrolatum is widely used in direct and indirect food applications. In the USA, the daily dietary exposure to petrolatum is estimated to be 0.404 mg/kg body-weight.(17)

For further information *see* Mineral Oil and Paraffin.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. For recommended occupational exposure limits *see* Mineral Oil and Paraffin.

16 Regulatory Status

GRAS listed. Accepted for use in certain food applications in many countries worldwide. Included in the FDA Inactive Ingredients Guide (ophthalmic preparations, oral capsules and tablets, otic, topical, and transdermal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Mineral oil; mineral oil light; paraffin; petrolatum and lanolin alcohols; white petrolatum.

White petrolatum

Synonyms: vaselinum album; white petroleum jelly; white soft paraffin.

Appearance: white petrolatum is a white to pale yellow-colored, translucent, soft unctuous mass. It is odorless and tasteless and not more than slightly fluorescent by daylight, even when melted.

Method of manufacture: white petrolatum is petrolatum that has been highly refined so that it is wholly or nearly decolorized.

Comments: white petrolatum is associated with fewer instances of hypersensitivity reactions and is the preferred petrolatum for use in cosmetics and pharmaceuticals, *see* Section 14.

18 Comments

Various grades of petrolatum are commercially available, which vary in their physical properties depending upon their source and refining process. Petrolatum obtained from different sources may therefore behave differently in a formulation.(18)

Care is required in heating petrolatum because of its large coefficient of thermal expansion. It has been shown by both rheological and spectrophotometric methods that petrolatum undergoes phase transition at temperatures between 30–40°C.

Additives, such as microcrystalline wax, may be used to add body to petrolatum. A specification for petrolatum is contained in the Food Chemicals Codex (FCC).

The EINECS number for petrolatum is 232-373-2.

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21 Authors

WJ Lambert.

22 Date of Revision

19 August 2005.

Petrolatum and Lanolin Alcohols

1 Nonproprietary Names

None adopted.

2 Synonyms

Amerchol CAB; *Forlan 500*; petrolatum and wool alcohols; white soft paraffin and lanolin alcohols; yellow soft paraffin and lanolin alcohols.

3 Chemical Name and CAS Registry Number

Petrolatum [8009-03-8] and
Lanolin alcohols [8027-33-6]

4 Empirical Formula and Molecular Weight

A mixture of petrolatum and lanolin alcohols.

5 Structural Formula

See Section 4.

6 Functional Category

Emollient; ointment base; plasticizer.

7 Applications in Pharmaceutical Formulation or Technology

Petrolatum and lanolin alcohols is a soft solid used in topical pharmaceutical formulations and cosmetics as an ointment base with emollient properties. It is also used in the preparation of creams and lotions. Petrolatum and lanolin alcohols can be used to absorb wound exudates. *See* Table I.

Table I: Uses of petrolatum and lanolin alcohols.

Use	Concentration (%)
Absorption base component	10.0–50.0
Emollient and plasticizer in ointments	5.0–50.0

8 Description

A pale ivory-colored, soft solid with a faint, characteristic sterol odor.

9 Pharmacopeial Specifications

—

10 Typical Properties

Acid value: $\leqslant 1$
Arsenic: $\leqslant 2$ ppm
Ash: $\leqslant 0.2\%$
Heavy metals: $\leqslant 20$ ppm
HLB value: ≈ 9
Hydroxyl value: 11–15
Melting range: 40–46°C
Microbiological count: the total bacterial count, when packaged, is less than 10 per gram of sample.
Moisture content: $\leqslant 0.2\%$
Saponification value: $\leqslant 2$
Solubility: soluble 1 in 20 parts of chloroform, and 1 in 100 parts of mineral oil; precipitates at higher concentrations. Precipitation occurs in ethanol (95%), hexane, and water. May be dispersed in isopropyl palmitate. Forms a gel in castor oil and corn oil.

11 Stability and Storage Conditions

Petrolatum and lanolin alcohols is stable and should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Lanolin alcohols is incompatible with coal tar, ichthammol, phenol, and resorcinol.

13 Method of Manufacture

Lanolin alcohols is blended with petrolatum.

14 Safety

Petrolatum and lanolin alcohols is generally regarded as an essentially nontoxic and nonirritant material. However, lanolin alcohols may be irritant to the skin and cause hypersensitivity in some individuals.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Accepted for use in topical pharmaceutical formulations and cosmetics. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Lanolin alcohols; lanolin alcohols ointment; mineral oil and lanolin alcohols; petrolatum.

Lanolin alcohols ointment

Synonyms: *Argobase EU*; wool alcohols ointment.
Appearance: white-colored ointment if prepared using white petrolatum, a yellow-colored ointment if yellow petrolatum is used in its preparation.
Comments: the BP 2004 describes lanolin alcohols ointment (wool alcohols ointment BP) as a mixture consisting of:

Lanolin alcohols 60 g
Paraffin 240 g

Yellow or white petrolatum 100 g
Mineral oil 600 g

However, the proportions of paraffin, petrolatum, and mineral oil may be varied to produce an ointment of the desired physical properties.

18 Comments

See individual monographs on Lanolin Alcohols, and Petrolatum for further information.

19 Specific References

—

20 General References

Davis SS. Viscoelastic properties of pharmaceutical semisolids I: ointment bases. *J Pharm Sci* 1969; 58: 412–418.

21 Authors

SC Owen.

22 Date of Revision

12 August 2005.

Phenol

1 Nonproprietary Names

BP: Phenol
JP: Phenol
PhEur: Phenolum
USP: Phenol

2 Synonyms

Carbolic acid; hydroxybenzene; oxybenzene; phenic acid; phenyl hydrate; phenyl hydroxide; phenylic acid; phenylic alcohol.

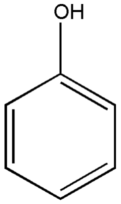
3 Chemical Name and CAS Registry Number

Phenol [108-95-2]

4 Empirical Formula and Molecular Weight

C_6H_6O 94.11

5 Structural Formula



6 Functional Category

Antimicrobial preservative; disinfectant.

7 Applications in Pharmaceutical Formulation or Technology

Phenol is used mainly as an antimicrobial preservative in parenteral pharmaceutical products. It has also been used in topical pharmaceutical formulations and cosmetics; *see* Table I.

Phenol is widely used as an antiseptic, disinfectant, and therapeutic agent, although it should not be used to preserve preparations that are to be freeze-dried.(1)

Table I: Uses of phenol.

Use	Concentration (%)
Disinfectant	5.0
Injections (preservative)	0.5
Local anesthetic	0.5–1.0
Mouthwash	⩽1.4

8 Description

Phenol occurs as colorless to light pink, caustic, deliquescent needle-shaped crystals or crystalline masses with a characteristic odor. When heated gently phenol melts to form a highly refractive liquid. The USP 28 permits the addition of a suitable stabilizer; the name and amount of substance used for this purpose must be clearly stated on the label.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for phenol.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Clarity of solution	+	+	+
Acidity	+	+	—
Congealing temperature	—	⩾39.5°C	⩾39°C
Water	—	—	⩽0.5%
Nonvolatile residue	⩽0.05%	⩽0.05%	⩽0.05%
Organic volatile impurities	—	—	+
Assay	⩾98.0%	99.0–100.5%	99.0–100.5%

10 Typical Properties

Acidity/alkalinity: pH = 6.0 (saturated aqueous solution)

Antimicrobial activity: phenol exhibits antimicrobial activity against a wide range of microorganisms such as Gram-negative and Gram-positive bacteria, mycobacteria and some fungi, and viruses; it is only very slowly effective against spores. Aqueous solutions of 1% w/v concentration are bacteriostatic, while stronger solutions are bactericidal. Phenol shows most activity in acidic solutions; increasing temperature also increases the antimicrobial activity. Phenol is inactivated by the presence of organic matter.

Autoignition temperature: 715°C

Boiling point: 181.8°C

Density: 1.071 g/cm^3

Dissociation constant: $pK_a = 10$ at 25°C

Flash point: 79°C (closed cup)

Explosive limits: 2% lower limit; 9% upper limit.

Freezing point: 40.9°C

Melting point: 43°C

Osmolarity: a 2.8% w/v solution is iso-osmotic with serum.

Partition coefficient: octanol:water = 1.46

Refractive index: $n_D^{41} = 1.5425$

Solubility: *see* Table III.

Vapor density (relative): 3.24 (air = 1)

Vapor pressure: 133 Pa (1 mmHg) at 40°C

11 Stability and Storage Conditions

When exposed to air and light, phenol turns a red or brown color, the color being influenced by the presence of metallic impurities. Oxidizing agents also hasten the color change. Aqueous solutions of phenol are stable. Oily solutions for

Table III: Solubility of phenol.

Solvent	Solubility at 20°C
Carbon disulfide	Very soluble
Chloroform	Very soluble
Ethanol (95%)	Very soluble
Ether	Very soluble
Fixed oils	Very soluble
Glycerin	Very soluble
Mineral oil	1 in 70
Volatile oils	Very soluble
Water	1 in 15

injection may be sterilized in hermetically sealed containers by dry heat. The bulk material should be stored in a well-closed, light-resistant container at a temperature not exceeding 15°C.

12 Incompatibilities

Phenol undergoes a number of chemical reactions characteristic of alcohols; however, it possesses a tautomeric enol structure that is weakly acidic. It will form salts with sodium hydroxide or potassium hydroxide, but not with their carbonates or bicarbonates.

Phenol is a reducing agent and is capable of reacting with ferric salts in neutral to acidic solutions to form a greenish-colored complex. Phenol decolorizes dilute iodine solutions, forming hydrogen iodide and iodophenol; stronger solutions of iodine react with phenol to form the insoluble 2,4,6-triiodophenol.

Phenol is incompatible with albumin and gelatin as they are precipitated. It forms a liquid or soft mass when triturated with compounds such as camphor, menthol, thymol, acetaminophen, phenacetin, chloral hydrate, phenazone, ethyl aminobenzoate, methenamine, phenyl salicylate, resorcinol, terpin hydrate, sodium phosphate, or other eutectic formers. Phenol also softens cocoa butter in suppository mixtures.

13 Method of Manufacture

Historically, phenol was produced by the distillation of coal tar. Today, phenol is prepared by one of several synthetic methods, such as the fusion of sodium benzenesulfonate with sodium hydroxide followed by acidification; the hydrolysis of chlorobenzene by dilute sodium hydroxide at high temperature and pressure to give sodium phenate, which on acidification liberates phenol (Dow process); or the catalytic vapor-phase reaction of steam and chlorobenzene at 500°C (Raschig process).

14 Safety

Phenol is highly corrosive and toxic, the main effects being on the central nervous system. The lethal human oral dose is estimated to be 1 g for an adult.

Phenol is absorbed from the gastrointestinal tract, skin, and mucous membranes and is metabolized to phenylglucuronide and phenyl sulfate, which are excreted in the urine.

Although there are a number of reports describing the toxic effects of phenol, these largely concern instances of accidental poisoning$^{(2,3)}$ or adverse reactions during its use as a therapeutic agent.$^{(4,5)}$ Adverse reactions associated with phenol used as a preservative are less likely owing to the smaller quantities that are used; however, it has been suggested that the body burden of phenol should not exceed 50 mg in a 10-hour period.$^{(6)}$ This amount could be exceeded following administration of large volumes of phenol-preserved medicines.

LD_{50} (mouse, IV): 0.11 g/kg$^{(7)}$
LD_{50} (mouse, oral): 0.3 g/kg
LD_{50} (rabbit, skin): 0.85 g/kg
LD_{50} (rat, skin): 0.67 g/kg
LD_{50} (rat, oral): 0.32 g/kg
LD_{50} (rat, SC): 0.46 g/kg

15 Handling Precautions

Phenol is toxic on contact with the skin or if swallowed or inhaled. Phenol is strongly corrosive, producing possibly irreversible damage to the cornea and severe skin burns, although the skin burns are painless owing to the anesthetic effects of phenol.

Phenol should be handled with caution, particularly when hot, owing to the release of corrosive and toxic fumes. The use of fume cupboards, enclosed plants, or other environmental containment is recommended. Protective polyvinyl chloride or rubber clothing is recommended, together with gloves, eye protection, and respirators. Spillages on the skin or eyes should be washed with copious amounts of water. Affected areas of the skin should be washed with water followed by application of a vegetable oil. Medical attention should be sought.

Phenol poses a slight fire hazard when cold and a moderate hazard when hot and exposed to heat or flame.

In the UK, the occupational exposure limits for phenol are 2 ppm long-term (8-hour TWA).$^{(8)}$ In the USA, the permissible exposure limit is 19 mg/m^3 long-term and the recommended exposure limits are 20 mg/m^3 long-term, and a maximum of 60 mg/m^3 short-term.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (injections). Included in medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Liquefied phenol.

Liquefied phenol

Appearance: liquefied phenol is phenol maintained as a liquid by the presence of approximately 10% water. It is a colorless liquid, with a characteristic aromatic odor, which may develop a red coloration on exposure to air and light.

Specific gravity: 1.065 at 25°C

Comments: liquefied phenol is often more convenient to use in a formulation than the crystalline form. However, liquefied phenol should not be used with fixed or mineral oils, although the crystalline solid may be used. Caution should be observed when handling liquified phenol to avoid contact with skin, as this could cause serious burns.

18 Comments

Although phenol is soluble in approximately 12 parts of water at ambient temperatures, larger amounts of phenol in water produce a two-phase system of phenol solution floating on a lower layer of wet phenol. At 20°C, 100 parts of phenol may be liquefied by the addition of 10 parts of water. At 84°C phenol is miscible with water in all proportions.

The EINECS number for phenol is 203-632-7.

19 Specific References

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20 General References

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21 Authors

RT Guest.

22 Date of Revision

23 August 2005.

Phenoxyethanol

1 Nonproprietary Names

BP: Phenoxyethanol
PhEur: Phenoxyethanolum
USPNF: Phenoxyethanol

2 Synonyms

Arosol; *Emerescence 1160*; ethyleneglycol monophenyl ether; β-hydroxyethyl phenyl ether; 1-hydroxy-2-phenoxyethane; *Phenoxen*; β-phenoxyethyl alcohol; phenyl cellulose.

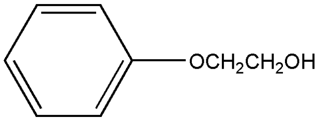
3 Chemical Name and CAS Registry Number

2-Phenoxyethanol [122-99-6]

4 Empirical Formula and Molecular Weight

$C_8H_{10}O_2$ 138.16

5 Structural Formula



6 Functional Category

Antimicrobial preservative; disinfectant.

7 Applications in Pharmaceutical Formulation or Technology

Phenoxyethanol is an antimicrobial preservative used in cosmetics and topical pharmaceutical formulations at a concentration of 0.5–1.0%; it may also be used as a preservative and antimicrobial agent for vaccines.(1,2) Therapeutically, a 2.2% solution or 2.0% cream has been used as a disinfectant for superficial wounds, burns, and minor infections of the skin and mucous membranes.(3–5)

Phenoxyethanol has a narrow spectrum of activity and is thus frequently used in combination with other preservatives, *see* Section 10.

8 Description

Phenoxyethanol is a colorless, slightly viscous liquid with a faint pleasant odor and burning taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for phenoxyethanol.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Refractive index	1.537–1.539	—
Relative density	1.105–1.110	1.105–1.110
Phenol	+	⩽0.1%
Chromatographic purity	—	+
Related substances	+	+
Assay	99.0–100.5%	98.0–102.0%

10 Typical Properties

Acidity/alkalinity: pH = 6.0 for a 1% v/v aqueous solution.
Antimicrobial activity: phenoxyethanol is an antibacterial preservative effective over a wide pH range against strains of *Pseudomonas aeruginosa* and to a lesser extent against *Proteus vulgaris* and other Gram-negative organisms. It is most frequently used in combination with other preservatives, such as parabens, to obtain a wider spectrum of antimicrobial activity.(6–8) *See also* Section 12. For reported minimum inhibitory concentrations (MICs) *see* Table II.(9)

Table II: Minimum inhibitory concentrations (MICs) of phenoxyethanol.

Microorganism	MIC (μg/mL)
Aspergillus niger ATCC 16404	3300
Candida albicans ATCC 10231	5400
Escherichia coli ATCC 8739	3600
Pseudomonas aeruginosa ATCC 9027	3200
Staphylococcus aureus ATCC 6538	8500

Autoignition temperature: 135°C
Boiling point: 245.2°C
Flash point: 121°C (open cup)
Melting point: 14°C
Partition coefficients:
Isopropyl palmitate : water = 2.9;
Mineral oil : water = 0.3;
Peanut oil : water = 2.6.
Refractive index: n_D^{20} = 1.537–1.539
Solubility: *see* Table III.
Specific gravity: 1.11 at 20°C

11 Stability and Storage Conditions

Aqueous phenoxyethanol solutions are stable and may be sterilized by autoclaving. The bulk material is also stable and should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

The antimicrobial activity of phenoxyethanol may be reduced by interaction with nonionic surfactants and possibly by

Table III: Solubility of phenoxyethanol.

Solvent	Solubility at 20°C
Acetone	Miscible
Ethanol (95%)	Miscible
Glycerin	Miscible
Isopropyl palmitate	1 in 26
Mineral oil	1 in 143
Olive oil	1 in 50
Peanut oil	1 in 50
Water	1 in 43

absorption by polyvinyl chloride.(10) The antimicrobial activity of phenoxyethanol against *Pseudomonas aeruginosa* may be reduced in the presence of cellulose derivatives (methylcellulose, sodium carboxymethylcellulose, and hypromellose (hydroxypropylmethylcellulose)).(11)

13 Method of Manufacture

Phenoxyethanol is prepared by treating phenol with ethylene oxide in an alkaline medium.

14 Safety

Phenoxyethanol produces a local anesthetic effect on the lips, tongue, and other mucous membranes. The pure material is a moderate irritant to the skin and eyes. In animal studies, a 10% v/v solution was not irritant to rabbit skin and a 2% v/v solution was not irritant to the rabbit eye.(12) Long-term exposure to phenoxyethanol may result in CNS toxic effects similar to other organic solvents.(13)

LD_{50} (rabbit, skin): 5 g/kg(14)
LD_{50} (rat, oral): 1.26 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Phenoxyethanol may be irritant to the skin and eyes; eye protection and gloves are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Chlorobutanol; chlorophenoxyethanol; phenoxypropanol.

Chlorophenoxyethanol

Empirical formula: $C_8H_9ClO_2$
Molecular weight: 172.60
CAS number: [29533-21-9]

Phenoxypropanol

Empirical formula: $C_9H_{12}O_2$
Molecular weight: 152.18
CAS number: [4169-04-4]
Synonyms: 1-phenoxypropan-2-ol.

18 Comments

Aqueous solutions are best prepared by shaking phenoxyethanol with hot water until dissolved, followed by cooling and adjusting the volume to the required concentration.

The EINECS number for phenoxyethanol is 204-589-7.

19 Specific References

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2 Lowe I, Southern J. The antimicrobial activity of phenoxyethanol in vaccines. *Lett Appl Microbiol* 1994; **18**(2): 115–116.
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21 Authors

SC Owen.

22 Date of Revision

17 August 2005.

Phenylethyl Alcohol

1 Nonproprietary Names

USP: Phenylethyl alcohol

2 Synonyms

Benzeneethanol; benzyl carbinol; benzylmethanol; β-hydroxyethyl benzene; PEA; phenethanol; β-phenylethyl alcohol; 2-phenylethyl alcohol; phenylethanol.

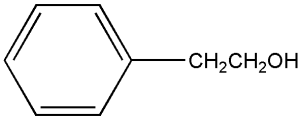
3 Chemical Name and CAS Registry Number

2-Phenylethanol [60-12-8]

4 Empirical Formula and Molecular Weight

$C_8H_{10}O$ 122.17

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

Phenylethyl alcohol is used as an antimicrobial preservative in nasal, ophthalmic, and otic formulations at 0.25–0.5% v/v concentration; it is generally used in combination with other preservatives.(1–3) Phenylethyl alcohol has also been used on its own as an antimicrobial preservative at concentrations up to 1% v/v in topical preparations. At this concentration, mycoplasmas are inactivated within 20 minutes, although enveloped viruses are resistant.(4) Phenylethyl alcohol is also used in flavors and as a perfumery component, especially in rose perfumes.

8 Description

Phenylethyl alcohol is a clear, colorless liquid with an odor of rose oil. It has a burning taste that irritates and then anesthetizes mucous membranes.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for phenylethyl alcohol.

Test	USP 28
Identification	+
Specific gravity	1.017–1.020
Refractive index	1.531–1.534
Residue on ignition	⩽0.005%
Chlorinated compounds	+
Aldehyde	+
Organic volatile impurities	+

10 Typical Properties

Antimicrobial activity: phenylethyl alcohol has moderate antimicrobial activity although it is relatively slow acting; it is not sufficiently active to be used alone.(5) Greatest activity occurs at less than pH 5; it is inactive above pH 8. Synergistic effects have been reported when combined with benzalkonium chloride, chlorhexidine gluconate or diacetate, polymyxin B sulfate, and phenylmercuric nitrate.(6–10) With either benzalkonium chloride or chlorhexidine, synergistic effects were observed against *Pseudomonas aeruginosa* and apparently additive effects against Gram-positive organisms. With phenylmercuric nitrate, the effect was additive against *Pseudomonas aeruginosa*. Additive effects against *Pseudomonas cepacia* in combination with either benzalkonium chloride or chlorhexidine have also been reported.(11) *See also* Section 12.

Bacteria: fair activity against Gram-positive bacteria; for *Staphylococcus aureus*, the minimum inhibitory concentration (MIC) may be more than 5 mg/mL. Greater activity is shown against Gram-negative organisms.(12) Typical MIC values are: *Salmonella typhi* 1.25 mg/mL; *Pseudomonas aeruginosa* 2.5 mg/mL; *Escherichia coli* 5.0 mg/mL.

Fungi: poor activity against molds and fungi.

Spores: inactive, e.g., at 0.6% v/v concentration, reported to be ineffective against spores of *Bacillus stearothermophilus* at 100°C for 30 minutes.

Boiling point: 219–221°C

Flash point: 102°C (open cup)

Melting point: −27°C

Partition coefficients:

Chloroform : water = 15.2;
Heptane : water = 0.58;
Octanol : water = 21.5.

Solubility: *see* Table II.

11 Stability and Storage Conditions

Phenylethyl alcohol is stable in bulk, but is volatile and sensitive to light and oxidizing agents. It is reasonably stable in both acidic and alkaline solutions. Aqueous solutions may be sterilized by autoclaving. If stored in low-density polyethylene containers, phenylethyl alcohol may be absorbed by the containers. Losses to polypropylene containers have been reported to be insignificant over 12 weeks at 30°C. Sorption to rubber closures is generally small.

Table II: Solubilty of phenylethyl alcohol.

Solvent	Solubility at 20°C
Benzyl benzoate	Very soluble
Chloroform	Very soluble
Diethyl phthalate	Very soluble
Ethanol (95%)	Very soluble
Ether	Very soluble
Fixed oils	Very soluble
Glycerin	Very soluble
Mineral oil	Slightly soluble
Propylene glycol	Very soluble
Water	1 in 60

The bulk material should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

Incompatible with oxidizing agents and protein, e.g., serum. Phenylethyl alcohol is partially inactivated by polysorbates, although this is not as great as the reduction in antimicrobial activity that occurs with parabens and polysorbates.(13)

13 Method of Manufacture

Phenylethyl alcohol is prepared by reduction of ethyl phenylacetate with sodium in absolute alcohol; by hydrogenation of phenylacetaldehyde in the presence of a nickel catalyst; or by addition of ethylene oxide or ethylene chlorohydrin to phenylmagnesium bromide, followed by hydrolysis. Phenylethyl alcohol also occurs naturally in a number of essential oils, especially rose oil.

14 Safety

Phenylethyl alcohol is generally regarded as a nontoxic and nonirritant material. However, at the concentration used to preserve eye-drops (about 0.5% v/v) or above, eye irritation may occur.(14)

LD_{50} (rabbit, skin): 0.79 g/kg(15)
LD_{50} (rat, oral): 1.79 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Phenylethyl alcohol is combustible when exposed to heat or flame, and emits acrid smoke when heated to decomposition. Eye protection and gloves are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (nasal, ophthalmic, and otic preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Chlorobutanol.

18 Comments

The EINECS number for phenylethyl alcohol is 200-456-2.

19 Specific References

1 Goldstein SW. Antibacterial agents in compounded ophthalmic solutions. *J Am Pharm Assoc* (*Pract Pharm*) 1953; **14**: 498–524.
2 Heller WM, Foss NE, Shay DE, Ichniowski CT. Preservatives in solutions. *J Am Pharm Assoc (Pract Pharm)* 1955; **16**: 29–36.
3 Hodges NA, Denyer SP, Hanlon GW, Reynolds JP. Preservative efficacy tests on formulated nasal products: reproducibility and factors affecting preservative activity. *J Pharm Pharmacol* 1996; **48**: 1237–1242.
4 Staal SP, Rowe WP. Differential effect of phenylethyl alcohol on mycoplasmas and enveloped viruses. *J Virol* 1974; **14**: 1620–1622.
5 Kohn SR, Gershenfeld L, Barr M. Effectiveness of antibacterial agents presently employed in ophthalmic preparations as preservatives against *Pseudomonas aeruginosa*. *J Pharm Sci* 1963; **52**: 967–974.
6 Richards RME, McBride RJ. Cross-resistance in *Pseudomonas aeruginosa* resistant to phenylethanol. *J Pharm Sci* 1972; **61**: 1075–1077.
7 Richards RME, McBride RJ. The preservation of ophthalmic solutions with antibacterial combinations. *J Pharm Pharmacol* 1972; **24**: 145–148.
8 Richards RME, McBride RJ. Effect of 3-phenylpropan-1-ol, 2-phenylethanol, and benzyl alcohol on *Pseudomonas aeruginosa*. *J Pharm Sci* 1973; **62**: 585–587.
9 Richards RME, McBride RJ. Enhancement of benzalkonium chloride and chlorhexidine acetate activity against *Pseudomonas aeruginosa* by aromatic alcohols. *J Pharm Sci* 1973; **62**: 2035–2037.
10 Richards RME, McBride RJ. Antipseudomonal effect of polymyxin and phenylethanol. *J Pharm Sci* 1974; **63**: 54–56.
11 Richards RME, Richards JM. *Pseudomonas cepacia* resistance to antibacterials. *J Pharm Sci* 1979; **68**: 1436–1438.
12 Lilley BD, Brewer JH. The selective antibacterial action of phenylethyl alcohol. *J Am Pharm Assoc (Sci)* 1953; **42**: 6–8.
13 Bahal CK, Kostenbauder HB. Interaction of preservatives with macromolecules V: binding of chlorobutanol, benzyl alcohol, and phenylethyl alcohol by nonionic agents. *J Pharm Sci* 1964; **53**: 1027–1029.
14 Boer Y. Irritation by eyedrops containing 2-phenylethanol. *Pharm Weekbl* (*Sci*) 1981; **3**: 826–827.
15 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 2879.

20 General References

Silver S, Wendt L. Mechanism of action of phenylethyl alcohol: breakdown of the cellular permeability barrier. *J Bacteriol* 1967; **93**: 560–566.

Sklubalova Z. Antimicrobial substances in ophthalmic drugs. *Ceska Slov Farm* 2004; 53(3): 107–116.

21 Authors

SC Owen.

22 Date of Revision

17 August 2005.

Phenylmercuric Acetate

1 Nonproprietary Names

BP: Phenylmercuric acetate
PhEur: Phenyldriargyri acetas
USPNF: Phenylmercuric acetate

2 Synonyms

(Acetato-*O*)phenylmercury; acetoxyphenylmercury; *Gallotox*; *Liquiphene*; phenylmercury acetate; PMA; PMAC; PMAS.

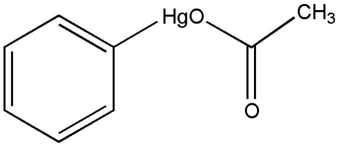
3 Chemical Name and CAS Registry Number

(Acetato)phenylmercury [62-38-4]

4 Empirical Formula and Molecular Weight

$C_8H_8HgO_2$ 336.74

5 Structural Formula



6 Functional Category

Antimicrobial preservative; antiseptic.

7 Applications in Pharmaceutical Formulation or Technology

Phenylmercuric acetate is used as an alternative antimicrobial preservative to phenylmercuric borate or phenylmercuric nitrate in cosmetics (in concentrations not exceeeding 0.0065% of mercury calculated as the metal) and pharmaceuticals. It may be used in preference to phenylmercuric nitrate owing to its greater solubility.

Phenylmercuric acetate is also used as a spermicide, *see* Table I.

See also Phenylmercuric Nitrate.

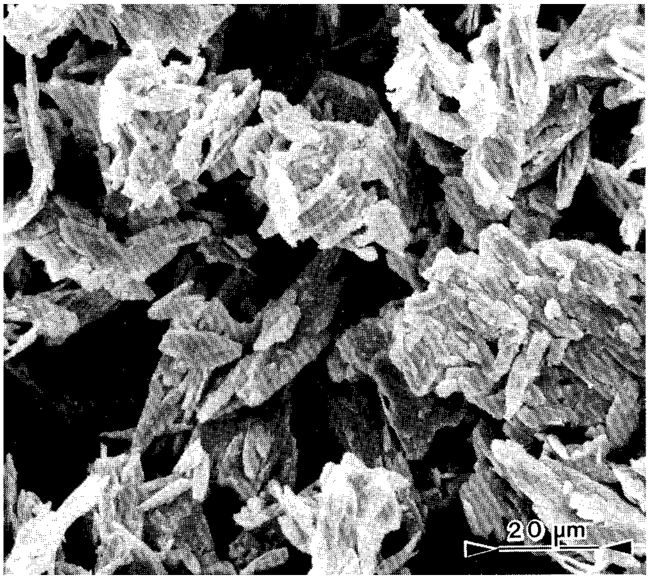
Table I: Uses of phenylmercuric acetate.

Use	Concentration (%)
Bactericide in parenterals and eye-drops	0.001–0.002
Spermicide in vaginal suppositories and jellies (active ingredient)	0.02

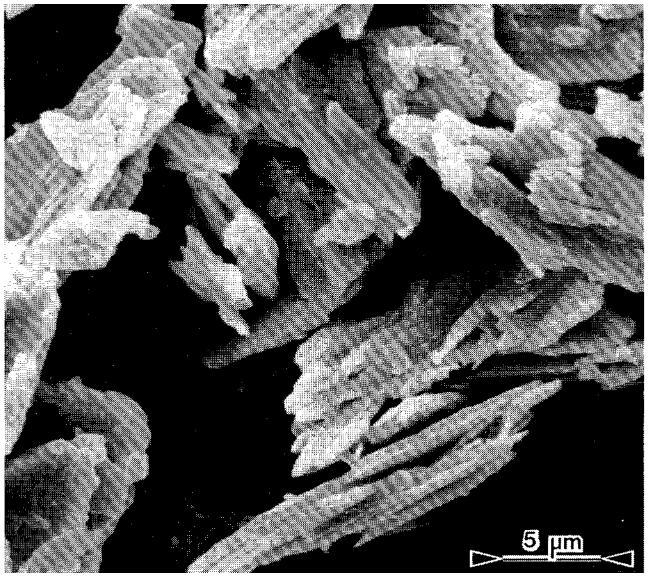
8 Description

Phenylmercuric acetate occurs as a white to creamy white, odorless or almost odorless, crystalline powder, or as small white prisms or leaflets.

SEM: 1
Excipient: Phenylmercuric acetate
Manufacturer: Eastman Fine Chemicals
Magnification: 600×



SEM: 2
Excipient: Phenylmercuric acetate
Manufacturer: Eastman Fine Chemicals
Magnification: 1800×



9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for phenylmercuric acetate.

Test	PhEur 2005	USPNF 23
Identification	+	+
Appearance of solution	+	—
Ionized mercury	⩽0.2%	+
Loss on drying	⩽0.5%	—
Polymercurated benzene compounds	⩽1.5%	⩽1.5%
Melting range	—	149–153°C
Residue on ignition	—	⩽0.2%
Organic volatile impurities	+	+
Assay	98.0–100.5%	98.0–100.5%

10 Typical Properties

Acidity/alkalinity: pH ≈4 for a saturated aqueous solution at 20°C.

Antimicrobial activity: phenylmercuric acetate is a broad-spectrum antimicrobial preservative with slow bactericidal and fungicidal activity similar to phenylmercuric nitrate; *see* Phenylmercuric Nitrate.

Dissociation constant: pK_a = 3.3

Melting point: 150°C

Partition coefficients:

Mineral oil : water = 0.1

Solubility: *see* Table III.

Table III: Solubility of phenylmercuric acetate.

Solvent	Solubility at 20°C[a]
Acetone	1 in 19
Chloroform	1 in 6.8
Ethanol (95%)	1 in 225
Ether	1 in 200
Water	1 in 180

[a] Compendial values for solubility vary considerably and in most instances do not show close agreement with laboratory-determined values, which also vary.

11 Stability and Storage Conditions

As for other phenylmercuric salts; *see* Phenylmercuric Nitrate.

Phenylmercuric acetate should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

As for other phenylmercuric salts; *see* Phenylmercuric Nitrate.

Incompatible with: halides; anionic emulsifying agents and suspending agents; tragacanth; starch; talc; sodium metabisulfite; sodium thiosulfate; disodium edetate; silicates; aluminum and other metals; amino acids; ammonia and ammonium salts; sulfur compounds; rubber; and some plastics.

Phenylmercuric acetate is reported to be incompatible with cefuroxime and ceftazidime.(1)

13 Method of Manufacture

Phenylmercuric acetate is readily formed by heating benzene with mercuric acetate.

14 Safety

Phenylmercuric acetate is mainly used as an antimicrobial preservative in topical pharmaceutical formulations. A number of adverse reactions to mercury- containing preservatives have been reported; *see* Phenylmercuric Nitrate.

LD_{50} (chicken, oral): 60 mg/kg(2)
LD_{50} (mouse, IP): 13 mg/kg
LD_{50} (mouse, IV): 18 mg/kg
LD_{50} (mouse, oral): 13 mg/kg
LD_{50} (mouse, SC): 12 mg/kg
LD_{50} (rat, oral): 41 mg/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Phenylmercuric acetate may be irritant to the skin, eyes, and mucous membranes. Eye protection, gloves, and a respirator are recommended. Chronic exposure via any route can lead to central nervous system damage. In the UK, the occupational exposure limit for mercury-containing compounds, calculated as mercury, is 0.01 mg/m^3 long-term (8-hour TWA) and 0.03 mg/m^3 short-term.(3)

16 Regulatory Status

Phenylmercuric acetate is no longer permitted to be used as a pesticide in the USA. It is, however, included in the FDA Inactive Ingredients Guide (ophthalmic preparations), and is also included in nonparenteral medicines licensed in the UK. In France, a maximum concentration of 0.01% is permitted for use in pharmaceuticals. The use of phenylmercuric acetate in cosmetics is restricted in the UK; *see* Phenylmercuric Nitrate. Included in the Canadian List of Acceptable Non-medicinal Ingredients (however, there must be no other suitable preservatives available).

17 Related Substances

Phenylmercuric borate; phenylmercuric nitrate; thimerosal.

18 Comments

The EINECS number for phenylmercuric acetate is 200-532-5.

19 Specific References

1 Hill DB, Barnes AR. Compatibility of phenylmercuric acetate with cefuroxime and ceftazidime eye drops. *Int J Pharm* 1997; **147**: 127–129.
2 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 33–34.
3 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.

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Abdelaziz AA, El-Nakeeb MA. Sporicidal activity of local anaesthetics and their binary combinations with preservatives. *J Clin Pharm Ther* 1988; **13**: 249–256.
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Grier N. Mercurials inorganic and organic. In: Block SS, ed. *Disinfection, Sterilization and Preservation,* 3rd edn. Philadelphia: Lea and Febiger, 1983: 346–374.

Hecht G. Ophthalmic preparations. In: Gennaro AR, ed. *Remington: The Science and Practice of Pharmacy*, 20th edn. Baltimore: Lippincott Williams and Wilkins, 2000: 821–835.

Parkin JE. The decomposition of phenylmercuric nitrate in sulphacetamide drops during heat sterilization. *J Pharm Pharmacol* 1993; **45**: 1024–1027.

Parkin JE, Button KL, Maroudas PA. The decomposition of phenylmercuric nitrate caused by disodium edetate in neomycin eye drops during the process of heat sterilization. *J Clin Pharm Ther* 1992; **17**: 191–196.

Parkin JE, Duffy MB, Loo CN. The chemical degradation of phenylmercuric nitrate by disodium edetate during heat sterilization at pH values commonly encountered in ophthalmic products. *J Clin Pharm Ther* 1992; **17**: 307–314.

21 Authors

SE Hepburn.

22 Date of Revision

17 August 2005.

Phenylmercuric Borate

1 Nonproprietary Names

BP: Phenylmercuric borate
PhEur: Phenylhydrargyri boras

2 Synonyms

(Dihydrogen borato)phenylmercury; phenylmercuriborate; phenylmercury borate; PMB.

3 Chemical Name and CAS Registry Number

[Orthoborato(3-)-O]-phenylmercurate(2-)dihydrogen [102-98-7]

The CAS Registry Number, chemical name and synonyms all refer to phenylmercuric borate alone, rather than the compound. The name phenylmercuric borate and the synonyms may, however, be applied to the PhEur 2005 material, which is a compound or a mixture of compounds, *see* Section 4. Unique CAS Registry Numbers for phenylmercuric borate and the compounds are as follows:

$C_6H_7BHgO_3$ [102-98-7]
$C_{12}H_{13}BHg_2O_4$ [8017-88-7]
$C_{12}H_{11}BHg_2O_3$ [6273-99-0]

4 Empirical Formula and Molecular Weight

The PhEur 2005 material is a compound consisting of equimolecular proportions of phenylmercuric hydroxide and phenylmercuric orthoborate ($C_{12}H_{13}BHg_2O_4$) or of the dehydrated form (metaborate, $C_{12}H_{11}BHg_2O_3$), or a mixture of the two compounds.

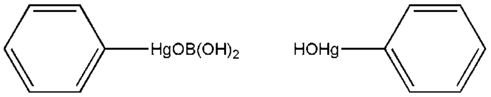
Phenylmercuric hydroxide and phenylmercuric orthoborate:

$C_{12}H_{13}BHg_2O_4$	633.2

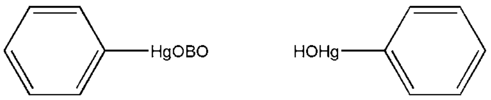
Phenylmercuric hydroxide and phenylmercuric metaborate:

$C_{12}H_{11}BHg_2O_3$	615.2

5 Structural Formula



Phenylmercuric orthoborate and phenylmercuric hydroxide



Phenylmercuric metaborate and phenylmercuric hydroxide

6 Functional Category

Antimicrobial preservative; antiseptic.

7 Applications in Pharmaceutical Formulation or Technology

Phenylmercuric borate is used as an alternative antimicrobial preservative to phenylmercuric acetate or phenylmercuric nitrate. It is more soluble than phenylmercuric nitrate and has also been reported to be less irritant than either phenylmercuric acetate or phenylmercuric nitrate.(1) *See* Table I.

See also Phenylmercuric Nitrate.

Table I: Uses of phenylmercuric borate.

Use	Concentration (%)
Antimicrobial agent in ophthalmics	0.002–0.004
Antimicrobial agent in parenterals	0.002

8 Description

Phenylmercuric borate occurs as colorless, shiny flakes or as a white or slightly yellow, odorless, crystalline powder.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for phenylmercuric borate.

Test	PhEur 2005
Identification	+
Appearance of solution	+
Ionized mercury (as heavy metals)	+
Loss on drying (at 45°C)	$\leqslant$3.5%
Assay (dried basis) of	
Mercury	64.5–66.0%
Borates (as H_3BO_3)	9.8–10.3%

10 Typical Properties

Acidity/alkalinity: pH = 5.0–7.0 for 0.6% w/v aqueous solution at 20°C.
Antimicrobial activity: phenylmercuric borate is a broad-spectrum antimicrobial preservative with slow bactericidal and fungicidal activity similar to that of phenylmercuric nitrate; *see* Phenylmercuric Nitrate.
Dissociation constant: $pK_a = 3.3$
Melting point: 112–113°C
Solubility: *see* Table III.

11 Stability and Storage Conditions

As for other phenylmercuric salts; *see* Phenylmercuric Nitrate. Solutions may be sterilized by autoclaving.

Phenylmercuric borate should be stored in a well-closed container, protected from light, in a cool, dry place.

Table III: Solubility of phenylmercuric borate.

Solvent	Solubility at 20°C[a] unless otherwise stated
Ethanol (95%)	1 in 150
Glycerin	Soluble
Propylene glycol	Soluble
Water	1 in 125
	1 in 100 at 100°C

[a] Compendial values for solubility vary considerably.

12 Incompatibilities

As for other phenylmercuric salts; *see* Phenylmercuric Nitrate.

Incompatible with: halides; anionic emulsifying agents and suspending agents; tragacanth; starch; talc; sodium metabisulfite; sodium thiosulfate; disodium edetate; silicates; aluminum and other metals; amino acids; ammonia and ammonium salts; sulfur compounds; rubber; and some plastics.

13 Method of Manufacture

Phenylmercuric borate may be prepared by heating mercuric borate with benzene or by evaporating to dryness, under vacuum, an alcoholic solution containing equimolar proportions of phenylmercuric hydroxide and boric acid.

14 Safety

Phenylmercuric borate is mainly used as an antimicrobial preservative in topical pharmaceutical formulations. A number of adverse reactions to mercury-containing preservatives have been reported; *see* Phenylmercuric Nitrate.

Although phenylmercuric borate is an irritant, it has been reported to be less so than either phenylmercuric acetate or phenylmercuric nitrate.(1) There is, however, some cross-sensitization potential with other mercurial preservatives.

Systemic absorption has been reported following regular use of a hand disinfectant soap containing 0.04% phenylmercuric borate, resulting in an increase in the estimated total daily body load of mercury from 30–100 μg per 24 hours.(2)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Phenylmercuric borate may be irritant to the skin, eyes, and mucous membranes. Eye protection, gloves, and a respirator are recommended. In the UK, the occupational exposure limit for mercury-containing compounds, calculated as mercury, is 0.01 mg/m^3 long-term (8-hour TWA) and 0.03 mg/m^3 short-term.(3)

16 Regulatory Status

Included in nonparenteral medicines licensed in Europe. In France, a maximum concentration of up to 0.01% is permitted for use in pharmaceutical formulations. In the UK, the use of phenylmercuric borate in cosmetics is restricted;(4) *see* Phenylmercuric Nitrate. Included in the Canadian List of Acceptable Non-medicinal Ingredients (ophthalmic, nasal and otic preparations; there must be no other suitable alternative preservative).

17 Related Substances

Phenylmercuric acetate; phenylmercuric nitrate; thimerosal.

18 Comments

The EINECS number for phenylmercuric borate is 203-068-1.

19 Specific References

1 Marzulli FN, Maibach HI. Antimicrobials: experimental contact sensitization in man. *J Soc Cosmet Chem* 1973; **24**: 399–421.
2 Peters-Haefeli L, Michod JJ, Aelhg A, *et al*. Urinary excretion of mercury after the use of an antiseptic soap containing 0.04% of phenylmercuric borate [in French]. *Schweiz Med Wochenschr* 1976; **106**(6): 171–178.
3 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.
4 Statutory Instrument (SI) 1989: No. 2233. Consumer Protection: The Consumer Products (Safety) Regulations 1989. London: HMSO, 1989.

20 General References

Abdelaziz AA, El-Nakeeb MA. Sporicidal activity of local anaesthetics and their binary combinations with preservatives. *J Clin Pharm Ther* 1988; **13**: 249–256.

Barkman R, Germanis M, Karpe G, Malmborg AS. Preservatives in eye drops. *Acta Ophthalmol* 1969; **47**: 461–475.

Grier N. Mercurials inorganic and organic. In: Block SS, ed. *Disinfection, Sterilization and Preservation,* 3rd edn. Philadelphia: Lea and Febiger, 1983: 346–374.

Hecht G. Ophthalmic preparations. In: Gennaro AR, ed. *Remington: The Science and Practice of Pharmacy*, 20th edn. Baltimore: Lippincott Williams and Wilkins, 2000: 821–835.

Parkin JE. The decomposition of phenylmercuric nitrate in sulphacetamide drops during heat sterilization. *J Pharm Pharmacol* 1993; **45**: 1024–1027.

Parkin JE, Button KL, Maroudas PA. The decomposition of phenylmercuric nitrate caused by disodium edetate in neomycin eye drops during the process of heat sterilization. *J Clin Pharm Ther* 1992; **17**: 191–196.

Parkin JE, Duffy MB, Loo CN. The chemical degradation of phenylmercuric nitrate by disodium edetate during heat sterilization at pH values commonly encountered in ophthalmic products. *J Clin Pharm Ther* 1992; **17**: 307–314.

21 Authors

SE Hepburn.

22 Date of Revision

17 August 2005.

Phenylmercuric Nitrate

1 Nonproprietary Names

BP: Phenylmercuric nitrate
PhEur: Phenylhydrargyri nitras
USPNF: Phenylmercuric nitrate

2 Synonyms

Basic phenylmercury nitrate; mercuriphenyl nitrate; merphenyl nitrate; nitratophenylmercury; phenylmercury nitrate; *Phe-Mer-Nite*; PMN.

Note that the synonyms above are usually used to refer to phenylmercuric nitrate alone. However, confusion with nomenclature and CAS Registry Number has led to these synonyms also being applied to the PhEur 2005 and USPNF 23 material, which is a compound of phenylmercuric nitrate and phenylmercuric hydroxide.

3 Chemical Name and CAS Registry Number

There are two CAS Registry Numbers associated with phenylmercuric nitrate. One refers to the mixture of phenylmercuric nitrate and phenylmercuric hydroxide ($C_{12}H_{11}Hg_2NO_4$) while the other refers to phenylmercuric nitrate alone ($C_6H_5HgNO_3$). The PhEur 2005, and USPNF 23 use the name phenylmercuric nitrate to describe the mixture and use the CAS Registry Number [55-68-5].

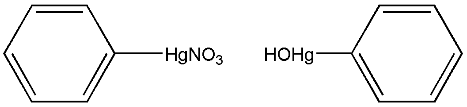
Hydroxyphenylmercury mixture with (nitrato-*O*)phenylmercury:
$C_{12}H_{11}Hg_2NO_4$ [8003-05-2]

(Nitrato-O)phenylmercury:
$C_6H_5HgNO_3$ [55-68-5]

4 Empirical Formula and Molecular Weight

$C_{12}H_{11}Hg_2NO_4$ 634.45

5 Structural Formula



6 Functional Category

Antimicrobial preservative; antiseptic.

7 Applications in Pharmaceutical Formulation or Technology

Phenylmercuric salts are used as antimicrobial preservatives mainly in ophthalmic preparations, but are also used in cosmetics (*see* Section 16), parenteral, and topical pharmaceutical formulations; *see* Table I.

Phenylmercuric salts are active over a wide pH range against bacteria and fungi and are usually used in neutral to alkaline solutions, although they have also been used effectively at slightly acid pH; *see* Section 10. In acidic formulations, phenylmercuric nitrate may be preferred to phenylmercuric acetate or phenylmercuric borate as it does not precipitate.

Phenylmercuric nitrate is also an effective spermicide, although its use in vaginal contraceptives is no longer recommended; *see* Section 14.

A number of adverse reactions to phenylmercuric salts have been reported and concern at the toxicity of mercury compounds may preclude the use of phenylmercuric salts under certain circumstances; *see* Section 14.

Table I: Uses of phenylmercuric nitrate.

Use	Concentration (%)
Bactericide in parenterals	0.001
Bactericide in vaginal suppositories and jellies	0.02
Preservative in eye drops	0.002

8 Description

Phenylmercuric nitrate PhEur 2005, and USPNF 23, is an equimolecular compound of phenylmercuric hydroxide and phenylmercuric nitrate; it occurs as a white, crystalline powder with a slight aromatic odor.

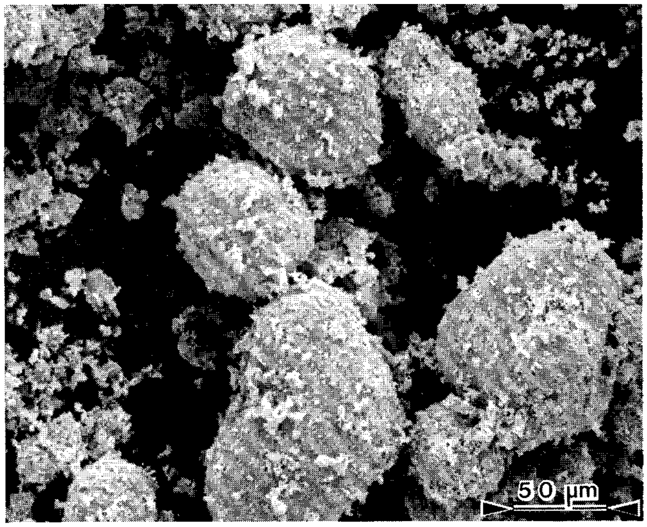
9 Pharmacopeial Specifications

See Table II.

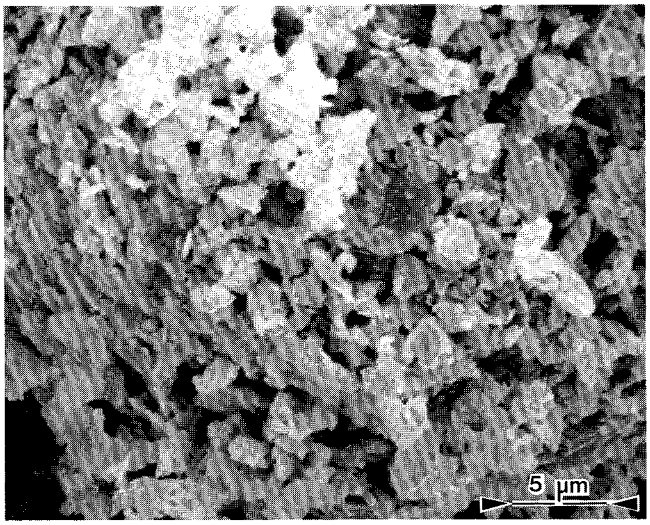
Table II: Pharmcopeial specifications for phenylmercuric nitrate.

Test	PhEur 2005	USPNF 23
Identification	+	+
Appearance of solution	+	—
Loss on drying	⩽1.0%	—
Residue on ignition	—	⩽0.1%
Mercury ions	—	+
Inorganic mercuric compounds	+	+
Organic volatile impurities	—	+
Assay (dried basis) of:		
Mercury	62.5–64.0%	62.75–63.50%
Phenylmercuric ion	—	87.0–87.9%

SEM: 1
Excipient: Phenylmercuric nitrate
Manufacturer: Eastman Fine Chemicals
Magnification: 180×



SEM: 2
Excipient: Phenylmercuric nitrate
Manufacturer: Eastman Fine Chemicals
Magnification: 1800×



10 Typical Properties

Acidity/alkalinity: a saturated aqueous solution is acidic to litmus.

Antimicrobial activity: phenylmercuric salts are broad-spectrum, growth-inhibiting agents at the concentrations normally used for the preservation of pharmaceuticals. They possess slow bactericidal and fungicidal activity. Antimicrobial activity tends to increase with increasing pH, although in solutions of pH 6 and below, activity against *Pseudomonas aeruginosa* has been demonstrated. Phenylmercuric salts are included in several compendial eye drop formulations of acid pH.

Activity is also increased in the presence of phenylethyl alcohol, and in the presence of sodium metabisulfite at acid pH. Activity is decreased in the presence of sodium metabisulfite at alkaline pH.(1–3) When used as preservatives in topical creams, phenylmercuric salts are active at pH 5–8.(4)

Bacteria (Gram-positive): good inhibition, more moderate cidal activity. Minimum inhibitory concentration (MIC) against *Staphylococcus aureus* is 0.5 μg/mL.

Bacteria (Gram-negative): inhibitory activity for most Gram-negative bacteria is similar to that for Gram-positive bacteria (MIC is approximately 0.3–0.5 μg/mL). Phenylmercuric salts are less active against some *Pseudomonas* species, and particularly *Pseudomonas aeruginosa* (MIC is approximately 12 μg/mL).

Fungi: most fungi are inhibited by 0.3–1 μg/mL; phenylmercuric salts exhibit both inhibitory and fungicidal activity; e.g., for phenylmercuric acetate against *Candida albicans*, MIC is 0.8 μg/mL; for phenylmercuric acetate against *Aspergillus niger*, MIC is approximately 10 μg/mL.

Spores: phenylmercuric salts may be active in conjunction with heat. The BP 1980 included heating at 100°C for 30 minutes in the presence of 0.002% w/v phenylmercuric acetate or phenylmercuric nitrate as a sterilization method. However, in practice this may not be sufficient to kill spores and heating with a bactericide no longer appears as a sterilization method in the BP 2004.

Dissociation constant: $pK_a = 3.3$

Melting point: 187–190°C with decomposition.

Partition coefficients:

Mineral oil : water = 0.58;
Peanut oil : water = 0.4.

Solubility: more soluble in the presence of either nitric acid or alkali hydroxides. *See* Table III.

Table III: Solubility of phenylmercuric nitrate.

Solvent	Solubility at 20°C[a] unless otherwise stated
Ethanol (95%)	1 in 1000
Fixed oils	Soluble
Glycerin	Slightly soluble
Water	1 in 600–1500
	1 in 160 at 100°C

[a] Compendial values for solubility vary considerably.

11 Stability and Storage Conditions

All phenylmercuric compound solutions form a black residue of metallic mercury when exposed to light or after prolonged storage. Solutions may be sterilized by autoclaving, although significant amounts of phenylmercuric salts may be lost, hence reducing preservative efficacy, owing to incompatibilities with packaging components or other excipients, e.g., sodium metabisulfite.(5–7) *See* Section 12.

Phenylmercuric nitrate should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

The antimicrobial activity of phenylmercuric salts may be reduced in the presence of anionic emulsifying agents and suspending agents, tragacanth, starch, talc, sodium metabisulfite,(8) sodium thiosulfate,(2) disodium edetate,(2) and silicates (bentonite, aluminum magnesium silicate, magnesium trisilicate, and kaolin).(9,10)

Phenylmercuric salts are incompatible with halides, particularly bromides and iodides, as they form less-soluble halogen compounds. At concentrations of 0.002% w/v precipitation may not occur in the presence of chlorides. Phenylmercuric salts are also incompatible with aluminum and other metals, ammonia and ammonium salts, amino acids, and with some sulfur compounds, e.g., in rubber.

Phenylmercuric salts are absorbed by rubber stoppers and some types of plastic packaging components; uptake is usually greatest to natural rubbers and polyethylene and least to polypropylene.(11–16)

Incompatibilities with some types of filter membranes may also result in loss of phenylmercuric salts following sterilization by filtration.(17)

13 Method of Manufacture

Phenylmercuric nitrate is readily formed by heating benzene with mercuric acetate, and treating the resulting acetate with an alkali nitrate.(18)

14 Safety

Phenylmercuric nitrate and other phenylmercuric salts are widely used as antimicrobial preservatives in parenteral and topical pharmaceutical formulations. However, concern over the use of phenylmercuric salts in pharmaceuticals has increased as a result of greater awareness of the toxicity of mercury and other mercury compounds. This concern must, however, be balanced by the effectiveness of these materials as antimicrobial preservatives and the low concentrations in which they are employed.

Phenylmercuric salts are irritant to the skin at 0.1% w/w concentration in petrolatum.(19) In solution, they may give rise to erythema and blistering 6–12 hours after administration. In a modified repeated insult patch test, a 2% w/v solution was found to produce extreme sensitization of the skin.(20,21)

Eye drops containing phenylmercuric nitrate as a preservative should not be used continuously for prolonged periods as mercurialentis, a brown pigmentation of the anterior capsule of the lens may occur. Incidence is 6% in patients using eye drops for greater than 6 years; however, the condition is not associated with visual impairment.(22,23) Cases of atypical band keratopathy have also been attributed to phenylmercuric nitrate preservative in eye drops.(24)

Concern that the absorption of mercury from the vagina may be harmful has led to the recommendation that phenylmercuric nitrate should not be used in intravaginal formulations.(25)

LD_{50} (mouse, IV): 27 mg/kg(26)
LD_{50} (mouse, oral): 50 mg/kg
LD_{50} (rat, SC): 63 mg/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Phenylmercuric nitrate may be irritant to the skin, eyes, and mucous membranes. Eye protection, gloves, and a respirator are recommended. In the UK, the occupational exposure limit for mercury-containing compounds, calculated as mercury, is 0.01 mg/m^3 long-term (8-hour TWA) and 0.03 mg/m^3 short-term.(27)

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IM and ophthalmic preparations). Included in nonparenteral medicines licensed in the UK. In the UK, the use of phenylmercuric salts in cosmetics is limited to 0.003% (calculated as mercury, equivalent to approximately 0.0047% of phenylmercuric nitrate) as a preservative in shampoos and hair creams, which contain nonionic emulsifiers that would render other preservatives ineffective. Total permitted concentration, as mercury, when mixed with other mercury compounds is 0.007% (equivalent up to approximately 0.011% of phenylmercuric nitrate).(28) Included in the Canadian List of Acceptable Non-medicinal Ingredients (ophthalmic, nasal and otic preparations only; there must be no other suitable alternative preservative).

17 Related Substances

Phenylmercuric acetate; phenylmercuric borate; thimerosal.

18 Comments

Phenylmercuric salts should be used in preference to benzalkonium chloride as a preservative for salicylates and nitrates and in solutions of salts of physostigmine and epinephrine that contain 0.1% sodium sulfite.

19 Specific References

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21 Authors

SE Hepburn.

22 Date of Revision

17 August 2005.

Phosphoric Acid

1 Nonproprietary Names

BP: Phosphoric acid
PhEur: Acidum phosphoricum concentratum
USPNF: Phosphoric acid
See also Section 17.

2 Synonyms

Acid fosforico; acide phosphorique; E338; hydrogen phosphate; syrupy phosphoric acid.

3 Chemical Name and CAS Registry Number

Orthophosphoric acid [7664-38-2]

4 Empirical Formula and Molecular Weight

H_3PO_4 98.00

5 Structural Formula

H_3PO_4

6 Functional Category

Acidifying agent.

7 Applications in Pharmaceutical Formulation or Technology

Phosphoric acid is widely used as an acidifying and buffering agent in a variety of pharmaceutical formulations. It is also widely used in food preparations as an acidulant, flavor, and synergistic antioxidant (0.001–0.005%) and sequestrant.

Therapeutically, dilute phosphoric acid has been used well-diluted in preparations used in the treatment of nausea and vomiting. Phosphoric acid 35% gel has also been used in dentistry to etch tooth enamel.

8 Description

Concentrated phosphoric acid occurs as a colorless, odorless, syrupy liquid.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for phosphoric acid.

	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Relative density	≈1.7	—
Sulfate	⩽100 ppm	+
Chloride	⩽50 ppm	—
Heavy metals	⩽10 ppm	⩽0.001%
Substances precipitated with ammonia	+	—
Arsenic	⩽2 ppm	—
Iron	⩽50 ppm	—
Alkali phosphates	—	+
Limit of nitrate	—	+
Phosphorous or hypophosphorous acid	+	+
Assay (of H_3PO_4)	84.0–90.0%	85.0–88.0%

10 Typical Properties

Acidity/alkalinity: pH = 1.6 (1% w/w aqueous solution)
Boiling point: 117.87°C
Dissociation constant:
$pK_{a1} = 2.15$;
$pK_{a2} = 7.09$;
$pK_{a3} = 12.32$.
Melting point: 42.35°C
Refractive index:
$n_D^{17.5} = 1.35846$ (30% w/w aqueous solution);
$n_D^{17.5} = 1.35032$ (20% w/w aqueous solution);
$n_D^{17.5} = 1.3423$ (10% w/w aqueous solution).
Solubility: miscible with ethanol (95%) and water with the evolution of heat.
Specific gravity:
1.874 (100% w/w) at 25°C;
1.6850 (85% w/w aqueous solution) at 25°C;
1.3334 (50% w/w aqueous solution) at 25°C;
1.0523 (10% w/w aqueous solution) at 25°C.

11 Stability and Storage Conditions

When stored at a low temperature, phosphoric acid may solidify, forming a mass of colorless crystals, comprised of the hemihydrate, which melt at 28°C. Phosphoric acid should be stored in an airtight container in a cool, dry place. Stainless steel containers may be used.

12 Incompatibilities

Phosphoric acid is a strong acid and reacts with alkaline substances. Mixtures with nitromethane are explosive.

13 Method of Manufacture

The majority of phosphoric acid is made by digesting phosphate rock (essentially tricalcium phosphate) with sulfuric acid; the phosphoric acid is then separated by slurry filtration.

Purification is achieved via chemical precipitation, solvent extraction, crystallization, or ion exchange.

14 Safety

In the concentrated form, phosphoric acid is an extremely corrosive and harmful acid. However, when used in pharmaceutical formulations it is usually very diluted and is generally regarded as an essentially nontoxic and nonirritant material.

The lowest lethal oral dose of concentrated phosphoric acid in humans is reported to be 1286 μL/kg.(1)

LD_{50} (rabbit, skin): 2.74 g/kg(1)
LD_{50} (rat, oral): 1.53 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Phosphoric acid is corrosive and can cause burns on contact with the skin, eyes and mucous membranes; contact should be avoided. Splashes should be washed with copious quantities of water. Protective clothing, gloves and eye protection are recommended.

Phosphoric acid is also irritant on inhalation. In the UK, the occupational exposure limit for phosphoric acid is 8 mg/m^3 long-term (8-hour TWA) and 2 mg/m^3 short-term (15-minutes).(2)

Phosphoric acid emits toxic fumes on heating.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (infusions, injections, oral solutions, topical creams, lotions, ointments and solutions, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Dilute phosphoric acid.

Dilute phosphoric acid

Synonyms: acidum phosphoricum dilutum; diluted phosphoric acid.

Comments: the PhEur 2005 states that dilute phosphoric acid contains 9.5–10.5% w/w H_3PO_4 and may be prepared by mixing phosphoric acid 115 g with 885 g of water. The USPNF 23 contains a monograph for diluted phosphoric acid and states that it contains 9.5–10.5% w/v H_3PO_4 and may be prepared by mixing phosphoric acid 69 mL with water to 1000 mL.

18 Comments

In the UK, a 1 in 330 aqueous solution of phosphoric acid is approved as a disinfectant for foot-and-mouth disease. A specification for phosphoric acid is contained in the Food Chemicals Codex (FCC).

The EINECS number for phosphoric acid is 231-633-2.

19 Specific References

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2 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002.* Sudbury: Health and Safety Executive, 2002.

20 General References

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21 Authors

WG Chambliss.

22 Date of Revision

8 August 2005.

Polacrilin Potassium

1 Nonproprietary Names

USPNF: Polacrilin potassium

2 Synonyms

Amberlite IRP-88; methacrylic acid polymer with divinylbenzene, potassium salt; polacrilinum kalii.

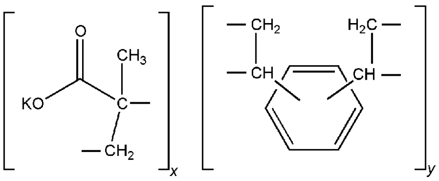
3 Chemical Name and CAS Registry Number

2-Methyl-2-propenoic acid polymer with divinylbenzene, potassium salt [39394-76-5]

4 Empirical Formula and Molecular Weight

See Sections 5,13 and 18.

5 Structural Formula



6 Functional Category

Tablet and capsule disintegrant.

7 Applications in Pharmaceutical Formulation or Technology

Polacrilin potassium is a cation-exchange resin used in oral pharmaceutical formulations as a tablet disintegrant.(1–3) Concentrations of 2–10% w/w have been used for this purpose although 2% w/w of polacrilin potassium is usually sufficient. Other polacrilin ion-exchange resins have been used as excipients to stabilize drugs, to mask or modify the taste of drugs, and in the preparation of sustained-release dosage forms(4) and drug carriers.

Polacrilin resins are also used in the analysis and manufacture of pharmaceuticals and food products.

8 Description

Polacrilin potassium occurs as a cream-colored, odorless and tasteless, free-flowing powder. Aqueous dispersions have a bitter taste.

9 Pharmacopeial Specifications

See Table I.

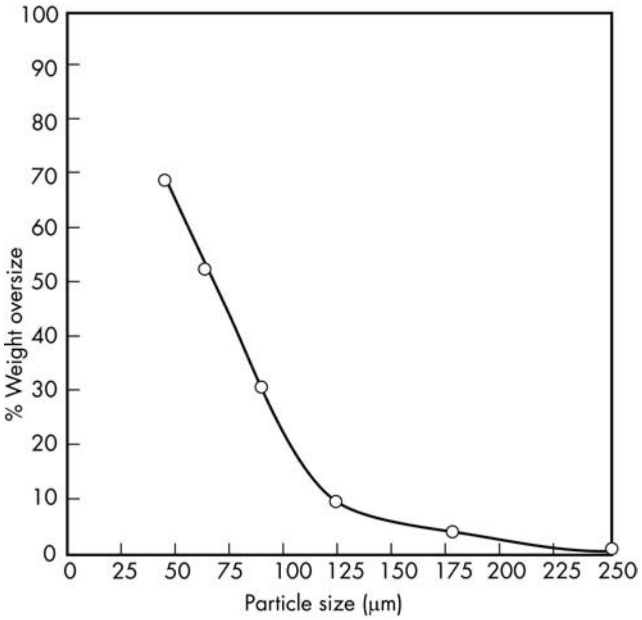


Figure 1: Particle size distribution of polacrilin potassium (Amberlite IRP-88).

Table I: Pharmacopeial specifications for polacrilin potassium.

Test	USPNF 23
Identification	+
Loss on drying	⩽10.0%
Powder fineness	⩽1.0% on a #100 mesh ⩽30.0% on a #200 mesh
Iron	⩽0.01%
Sodium	⩽0.20%
Heavy metals	⩽0.002%
Organic volatile impurities	+
Assay of potassium (dried basis)	20.6%–25.1%

10 Typical Properties

Density (bulk): 0.48 g/cm^3 for *Amberlite IRP-88*.(3)
Density (tapped): 0.62 g/cm^3 for *Amberlite IRP-88*.(3)
Particle size distribution: *see* Figure 1.(3)
Solubility: practically insoluble in water and most other liquids, although polacrilin resins swell rapidly when wetted.

11 Stability and Storage Conditions

Polacrilin potassium and other polacrilin resins are stable to light, air, and heat up to their maximum operation temperature; *see* Table II. Excessive heating can cause thermal decomposition of the resins and may yield one or more oxides of carbon, nitrogen, sulfur, and/or amines.

Table II: Summary of physicochemical properties of pharmaceutical grade *Amberlite* resins.

Amberlite grade	Copolymer	Type	Functional structure	Ionic form	Particle size (mesh)	Parent resin	Maximum moisture (%)	pH range	Maximum temperature (°C)	Application
Cation-exchange resins										
IRP-69	Styrene and DVB[a]	Strongly acidic	$SO_3^-Na^+$	Na^+	100–500	*IR-120*	10	0–14	120	Carrier for cationic drugs that are bases or salts
IRP-64	Methacrylic acid and DVB	Weakly acidic	COO^-H^+	H^+	100–500	*IRC-50*	10	5–14	120	Carrier for cationic drugs
IRP-88	Methacrylic acid and DVB	Weakly acidic	COO^-K^+	K^+	100–500	*IRC-50*	10	5–14	120	Tablet disintegrant
Anion-exchange resins										
IRP-58	Phenolic polyamine	Weakly basic	NH_2NH_2	Free base	100–500	*IR-4B*	10	0–7	60	Carrier for anionic drugs that are acids
IRP-67	Styrene and DVB	Strongly basic	$N(CH_3)_3^+Cl^-$	Cl^-	100–500	*IRA-400*	10	0–12	60	Carrier for anionic drugs that are acids or salts

Note that all of the above grades, with the exception of *Amberlite IRP-88*, are available in particle-size grades <325 mesh.

[a] DVB: divinylbenzene.

Polacrilin resins should be stored in well-closed containers in a cool, dry place.

12 Incompatibilities

Incompatible with strong oxidizing agents, amines, particularly tertiary amines, and some other substances that interact with polacrilin resins.(5)

13 Method of Manufacture

Polacrilin resin (*Amberlite IRP-64*) is prepared by the copolymerization of methacrylic acid with divinylbenzene (DVB). Polacrilin potassium (*Amberlite IRP-88*) is then produced by neutralizing this resin with potassium hydroxide.

Other resins are similarly produced by copolymerization between styrene and divinylbenzene (*Amberlite IRP-69*, *Amberlite IRP-67*, *Amberlite IR-120*, and *Amberlite IRA-400*). Phenolic-based polyamine condensates (*Amberlite IRP-58*) may also be produced.

The homogeneity of the resin structure depends on the purity, nature, and properties of the copolymers used as well as the controls and conditions employed during the polymerization reaction. The nature and degree of crosslinking have significant influence on the physicochemical properties of the resin matrix. The functional groups introduced on the matrix confer the property of ion exchange. Depending upon the acidity or basicity of the functional groups, strongly acidic to strongly basic types of ion-exchange resins may be produced.

14 Safety

Polacrilin potassium and other polacrilin resins are used in oral pharmaceutical formulations and are generally regarded as nontoxic and nonirritant materials. However, excessive ingestion of polacrilin resins may disturb the electrolyte balance of the body.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Polacrilin potassium may be irritating to the eyes; eye protection and gloves are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in non-parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Polacrilin.

Polacrilin

CAS number: [54182-62-6]

Synonyms: *Amberlite IRP-64*; methacrylic acid polymer with divinylbenzene; 2-methyl-2-propenoic acid polymer with divinylbenzene.

See also Section 18.

18 Comments

A number of other polacrilin (*Amberlite*) resins are commercially available that have a variety of industrial and pharmaceutical applications; *see* Table II.

19 Specific References

1 Van Abbé NJ, Rees JT. Amberlite resin XE-88 as a tablet disintegrant. *J Am Pharm Assoc (Sci)* 1958; 47: 487–489.

2 Khan KA, Rhodes CT. Effect of disintegrant concentration on disintegration and compression characteristics of two insoluble direct compression systems. *Can J Pharm Sci* 1973; 8: 77–80.

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5 Borodkin S, Yunker MH. Interaction of amine drugs with a polycarboxylic acid ion-exchange resin. *J Pharm Sci* 1970; **59**: 481–486.

20 General References

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21 Authors

A Palmieri.

22 Date of Revision

8 August 2005.

Poloxamer

1 Nonproprietary Names

BP: Poloxamers
PhEur: Poloxamera
USPNF: Poloxamer

2 Synonyms

Lutrol; *Monolan*; *Pluronic*; poloxalkol; polyethylene–propylene glycol copolymer; polyoxyethylene–polyoxypropylene copolymer; *Supronic*; *Synperonic*.

3 Chemical Name and CAS Registry Number

α-Hydro-ω-hydroxypoly(oxyethylene)poly(oxypropylene) poly(oxyethylene) block copolymer [9003-11-6]

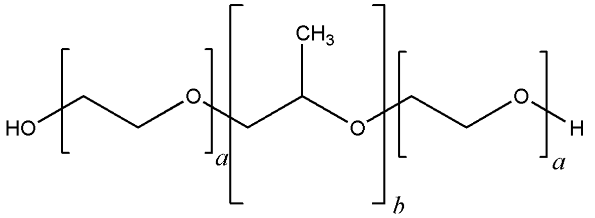
4 Empirical Formula and Molecular Weight

The poloxamer polyols are a series of closely related block copolymers of ethylene oxide and propylene oxide conforming to the general formula $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$. The grades included in the PhEur 2005 and USPNF 23 are shown in Table I. The PhEur 2005 states that a suitable antioxidant may be added.

Table I: Typical poloxamer grades.

Poloxamer	Physical form	*a*	*b*	Average molecular weight
124	Liquid	12	20	2 090–2 360
188	Solid	80	27	7 680–9 510
237	Solid	64	37	6 840–8 830
338	Solid	141	44	12 700–17 400
407	Solid	101	56	9 840–14 600

5 Structural Formula



6 Functional Category

Dispersing agent; emulsifying and coemulsifying agent; solubilizing agent; tablet lubricant; wetting agent.

7 Applications in Pharmaceutical Formulation or Technology

Poloxamers are nonionic polyoxyethylene–polyoxypropylene copolymers used primarily in pharmaceutical formulations as emulsifying or solubilizing agents.(1–8) The polyoxyethylene segment is hydrophilic while the polyoxypropylene segment is hydrophobic. All of the poloxamers are chemically similar in composition, differing only in the relative amounts of propylene and ethylene oxides added during manufacture. Their physical and surface-active properties vary over a wide range and a number of different types are commercially available; *see* Sections 4,9,10 and 18.

Poloxamers are used as emulsifying agents in intravenous fat emulsions, and as solubilizing and stabilizing agents to maintain the clarity of elixirs and syrups. Poloxamers may also be used as wetting agents; in ointments, suppository bases, and gels; and as tablet binders and coatings.

Poloxamer 188 has also been used as an emulsifying agent for fluorocarbons used as artificial blood substitutes and in the preparation of solid-dispersion systems.

More recently, poloxamers have found use in drug-delivery systems.(9–14)

Therapeutically, poloxamer 188 is administered orally as a wetting agent and stool lubricant in the treatment of constipation; it is usually used in combination with a laxative such as danthron. Poloxamers may also be used therapeutically as wetting agents in eye-drop formulations, in the treatment of kidney stones, and as skin-wound cleansers.

Poloxamer 338 and 407 are used in solutions for contact lens care. *See* Table II.

Table II: Uses of poloxamer.

Use	Concentration (%)
Fat emulsifier	0.3
Flavor solubilizer	0.3
Fluorocarbon emulsifier	2.5
Gelling agent	15–50
Spreading agent	1
Stabilizing agent	1–5
Suppository base	4–6 or 90
Tablet coating	10
Tablet excipient	5–10
Wetting agent	0.01–5

8 Description

Poloxamers generally occur as white, waxy, free-flowing prilled granules, or as cast solids. They are practically odorless and tasteless. At room temperature, poloxamer 124 occurs as a colorless liquid.

9 Pharmacopeial Specifications

See Table III.

10 Typical Properties

Acidity/alkalinity: pH = 5.0–7.4 for a 2.5% w/v aqueous solution.

Cloud point: >100°C for a 1% w/v aqueous solution, and a 10% w/v aqueous solution of poloxamer 188.

Table III: Pharmacopeial specifications for poloxamer.

Test	PhEur 2005	USPNF 23
Identification	+	—
Characters	+	—
Appearance of solution	+	—
Average molecular weight		
For poloxamer 124	2 090–2 360	2 090–2 360
For poloxamer 188	7 680–9 510	7 680–9 510
For poloxamer 237	6 840–8 830	6 840–8 830
For poloxamer 338	12 700–17 400	12 700–17 400
For poloxamer 407	9 840–14 600	9 840–14 600
Weight percent oxyethylene		
For poloxamer 124	44.8–48.6	46.7 ± 1.9
For poloxamer 188	79.9–83.7	81.8 ± 1.9
For poloxamer 237	70.5–74.3	72.4 ± 1.9
For poloxamer 338	81.4–84.9	83.1 ± 1.7
For poloxamer 407	71.5–74.9	73.2 ± 1.7
pH (aqueous solution)	5.0–7.5	5.0–7.5
Unsaturation (mEq/g)		
For poloxamer 124	—	0.020 ± 0.008
For poloxamer 188	—	0.026 ± 0.008
For poloxamer 237	—	0.034 ± 0.008
For poloxamer 338	—	0.031 ± 0.008
For poloxamer 407	—	0.048 ± 0.017
Oxypropylene:oxyethylene ratio	+	—
Total ash	⩽0.4%	—
Heavy metals	—	⩽0.002%
Organic volatile impurities	—	+
Water	⩽1.0%	—
Free ethylene oxide, propylene oxide and 1,4-dioxane	+	+
Ethylene oxide	—	⩽1 ppm
Propylene oxide	—	⩽5 ppm
1,4-Dioxane	—	⩽5 ppm

Density: 1.06 g/cm^3 at 25°C
Flash point: 260°C
Flowability: solid poloxamers are free flowing.
HLB value: 0.5–30; 29 for poloxamer 188.
Melting point:
16°C for poloxamer 124;
52–57°C for poloxamer 188;
49°C for poloxamer 237;
57°C for poloxamer 338;
52–57°C for poloxamer 407.
Moisture content: poloxamers generally contain less than 0.5% w/w water and are hygroscopic only at relative humidity greater than 80%. *See also* Figure 1.
Solubility: solubility varies according to the poloxamer type; *see also* Table IV.

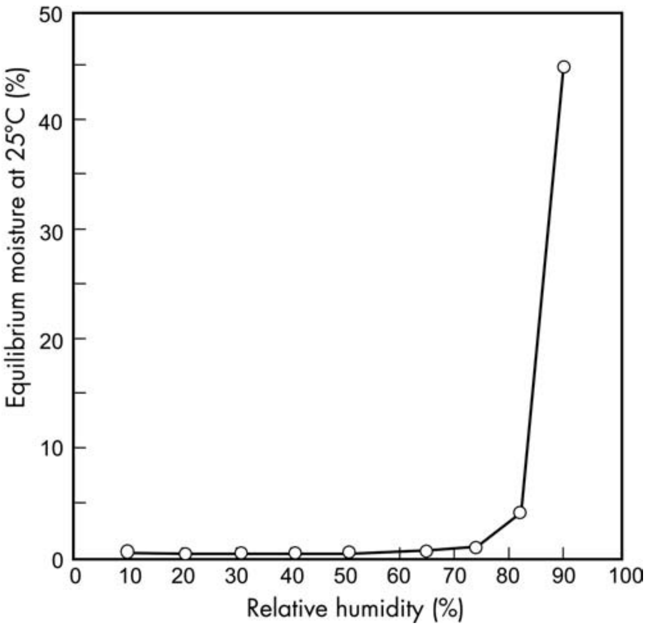


Figure 1: Equilibrium moisture content of poloxamer 188 (*Pluronic F-68*).

Surface tension:
19.8 mN/m (19.8 dynes/cm) for a 0.1% w/v aqueous poloxamer 188 solution at 25°C;
24.0 mN/m (24.0 dynes/cm) for a 0.01% w/v aqueous poloxamer 188 solution at 25°C;
26.0 mN/m (26.0 dynes/cm) for a 0.001% w/v aqueous poloxamer solution at 25°C.
Viscosity (dynamic): 1000 mPa s (1000 cP) as a melt at 77°C for poloxamer 188.

11 Stability and Storage Conditions

Poloxamers are stable materials. Aqueous solutions are stable in the presence of acids, alkalis, and metal ions. However, aqueous solutions support mold growth.

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Depending on the relative concentrations, poloxamer 188 is incompatible with phenols and parabens.

Table IV: Solubility at 20°C for various types of poloxamer in different solvents.

Type	Solvent				
	Ethanol (95%)	Propan-2-ol	Propylene glycol	Water	Xylene
Poloxamer 124	Freely soluble	Freely soluble	Freely soluble	Freely soluble	Freely soluble
Poloxamer 188	Freely soluble	—	—	Freely soluble	—
Poloxamer 237	Freely soluble	Sparingly soluble	—	Freely soluble	Sparingly soluble
Poloxamer 338	Freely soluble	—	Sparingly soluble	Freely soluble	—
Poloxamer 407	Freely soluble	Freely soluble	—	Freely soluble	—

13 Method of Manufacture

Poloxamer polymers are prepared by reacting propylene oxide with propylene glycol to form polyoxypropylene glycol. Ethylene oxide is then added to form the block copolymer.

14 Safety

Poloxamers are used in a variety of oral, parenteral, and topical pharmaceutical formulations and are generally regarded as nontoxic and nonirritant materials. Poloxamers are not metabolized in the body.

Animal toxicity studies, with dogs and rabbits, have shown poloxamers to be nonirritating and nonsensitizing when applied in 5% w/v and 10% w/v concentration to the eyes, gums, and skin.

In a 14-day study of intravenous administration at concentrations up to 0.5 g/kg/day to rabbits, no overt adverse effects were noted. A similar study with dogs also showed no adverse effects at dosage levels up to 0.5 g/kg/day. In a longer-term study, rats fed 3% w/w or 5% w/w of poloxamer in food for up to 2 years did not exhibit any significant symptoms of toxicity. However, rats receiving 7.5% w/w of poloxamer in their diet showed some decrease in growth rate.

No hemolysis of human blood cells was observed over 18 hours at 25°C, with 0.001–10% w/v poloxamer solutions.

Acute animal toxicity data for poloxamer 188:(15)

LD_{50} (mouse, IV): 1 g/kg
LD_{50} (mouse, oral): 15 g/kg
LD_{50} (mouse, SC): 5.5 g/kg
LD_{50} (rat, IV): 7.5 g/kg
LD_{50} (rat, oral): 9.4 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IV injections; inhalations, ophthalmic preparations; oral powders, solutions, suspensions, and syrups; topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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18 Comments

Although the USPNF 23 contains specifications for five poloxamer grades, many more different poloxamers are commercially available that vary in their molecular weight and the proportion of oxyethylene present in the polymer. A series of poloxamers with greatly varying physical properties are thus available.

The nonproprietary name 'poloxamer' is followed by a number, the first two digits of which, when multiplied by 100, correspond to the approximate average molecular weight of the polyoxypropylene portion of the copolymer and the third digit, when multiplied by 10, corresponds to the percentage by weight of the polyoxyethylene portion.

Similarly, with many of the trade names used for poloxamers, e.g. *Pluronic F-68* (BASF Corp), the first digit arbitrarily represents the molecular weight of the polyoxypropylene portion and the second digit represents the weight percent of the oxyethylene portion. The letters 'L', 'P', and 'F', stand for the physical form of the poloxamer: liquid, paste, or flakes; *see also* Table V.

Table V: Nonproprietary name and corresponding commercial grade.

Nonproprietary name	Commercial grade
Poloxamer 124	L-44
Poloxamer 188	F-68
Poloxamer 237	F-87
Poloxamer 338	F-108
Poloxamer 407	F-127

Note that in the USA the trade name *Pluronic* is used by BASF Corp. for pharmaceutical-grade and industrial-grade poloxamers, while in Europe the trade name *Lutrol* is used by BASF Corp. for the pharmaceutical-grade material.

Poloxamers for use in the cosmetic industry as oil-in-water emulsifiers, cleansers for mild facial products, and dispersing agents are marketed by BASF Corp. as *Pluracare*. The grades available are listed in Table VI. Poloxamer has been used in a poly(lactic-co-glycolic acid) (PLGA):poloxamer and PLGA:poloxamine blend nanoparticle composition as novel carriers for gene delivery.(16) A specification for poloxamer is contained in the Food Chemicals Codex (FCC).

Table VI: Nonproprietary name and corresponding *Pluracare* grade (BASF Corp.).

Nonproprietary name	Commercial grade	HLB value	pH of 2.5% w/v aqueous solution
Poloxamer 184	L-64	12–18	5–7.5
Poloxamer 185	P-65	12–18	6–7.4
Poloxamer 407	F-127	18–23	6–7.4

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20 General References

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21 Authors

JH Collett.

22 Date of Revision

26 August 2005.

Polycarbophil

1 Nonproprietary Names

USP: Polycarbophil

2 Synonyms

Noveon AA-1.

3 Chemical Name and CAS Registry Number

Polycarbophil [9003-01-4]

4 Empirical Formula and Molecular Weight

Polycarbophils are polymers of acrylic acid crosslinked with divinyl glycol. The molecular weight of these polymers is theoretically estimated to range from 700 000 to 3–4 billion. However, there are no methods currently available to measure the actual molecular weight of a crosslinked (i.e. three-dimensional) polymer of this type.

5 Structural Formula

See Section 4.

6 Functional Category

Adsorbent; bioadhesive; controlled-release tablet binder; emulsifying agent; thickening agent; suspending agent.

7 Applications in Pharmaceutical Formulation or Technology

Conventionally, polycarbophil is used as a thickening agent at very low concentrations (less than 1%) to produce a wide range of viscosities and flow properties in topical lotions, creams, and gels, in oral suspensions, and in transdermal gel reservoirs. It is also used as an emulsifying agent in topical oil-in-water systems.

Polycarbophil is an excellent bioadhesive in buccal, ophthalmic, intestinal, nasal, vaginal, and rectal applications. Buccal tablets prepared using polycarbophil have shown high bioadhesive force and prolonged residence time and proved to be nonirritative in *in vivo* trials with human buccal mucosa.(1) It is also useful in designing controlled-release formulations(2) and for drugs that undergo first-pass metabolism.(3) Polycarbophil buccoadhesive disks have also been developed in formulations increasing the bioavailability(4) and transmucosal absorption of poorly water-soluble drugs.(5) Sublingual tablets of buprenorphine formulated using polycarbophil have shown superior mucoadhesive strength when compared to those using carbomer.(6)

Polycarbophil gels have been used for delivering bioactive substances for local application to gingival,(7) oropharyngeal(8) and periodontal(9,10) areas and also for ocular drug delivery.(11) The nasal retention of plasmid DNA is highly prolonged with the use of polycarbophil as the gelling agent.(12) Polycarbophil has also been used to design an insulin liquid suppository for rectal application.(13,14) A vaginal gel of econazole has shown improved therapeutic benefit on topical application in vaginal candidiasis.(15) Mucoadhesive vaginal vaccine delivery systems using polycarbophil have proved to be effective in the induction of mucosal and systemic immune responses.(16) Polycarbophil gels have been used to deliver granulocyte-macrophage colony-stimulating factor (GM-CSF) effectively to genital preneoplastic lesions.(17) Polycarbophil microspheres have been formulated for drug delivery to oral(18,19) and nasal(20) cavities. Floating-bioadhesive microspheres coated with polycarbophil have been found to be a useful gastroretentive drug delivery system for the treatment of *Helicobacter pylori*.(21) Conjugation with L-cysteine greatly enhances the mucoadhesive properties of polycarbophil(22) and can be used as a platform for oral polypeptide delivery(23) (e.g. heparin,(24) insulin,(25) antigens for oral protein vaccination(26)) and for ocular(27) and transdermal drug delivery systems.(28) Polycarbophil has been reported to act as a permeation enhancer by triggering the reversible opening of the tight junctions between the cells, thereby allowing the paracellular transport of peptides, in addition to locally deactivating the most important enzymes of the gastrointestinal tract.(29) Polycarbophil promotes bowel regularity and is used therapeutically for chronic constipation, diverticulosis, and irritable bowel syndrome.

8 Description

Polycarbophil occurs as fluffy, white to off-white, mildly acidic polymer powder with slightly acetic odor.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for polycarbophil.

Test	USP 28
Identification	+
pH (1% dispersion)	$\leqslant$4.0
Loss on drying	$\leqslant$1.5%
Absorbing power	$\geqslant$62 g/g
Limit of acrylic acid	$\leqslant$0.3%
Limit of ethyl acetate	$\leqslant$0.45%
Organic volatile impurities	+
Residue on ignition	$\leqslant$4.0%

10 Typical Properties

Acidity/alkalinity: pH = 2.5–3.0 (1.0% w/v aqueous dispersion); pH = 2.7–3.5 (0.5% w/v aqueous dispersion).

Ash content: 0.009 ppm

Density (bulk): 0.19–0.24 g/cm^3

Dissociation constant: pK_a = 6.0 ± 0.5

Equilibrium moisture content: 8–10% (at 50% relative humidity)

Glass transition temperature: 100–105°C

Moisture content: 2.0% maximum

Solubility: polycarbophil polymers can swell in water to around 1000 times their original volume (and ten times their original diameter) to form gels when exposed to a pH environment above 4–6. Since the pK_a of these polymers is 6.0 ± 0.5, the carboxylate groups on the polymer backbone ionize, resulting in electrostatic repulsion between the negative particles, which extends the molecule, adding to the swelling of the polymer.

Particle size distribution: polycarbophils are produced from primary polymer particles of an average diameter of about 0.2 μm. These polymers are then flocculated, resulting in powders averaging 2–7 μm in diameter. Once formed, the flocculated agglomerates cannot be broken down into their primary particles.

Specific gravity: 1.41

11 Stability and Storage Conditions

Polycarbophil polymers are stable, hygroscopic materials. They do not undergo hydrolysis or oxidation under normal conditions. Heat aging at temperatures below 104°C for up to 2 hours does not affect the efficiency of the dry polymer. However, prolonged exposure to excessive temperatures can result in discoloration, reduced stability, and in some cases plasticization of the polymer. Complete decomposition occurs with heating for 30 minutes at 260°C.

Polycarbophil polymers do not support bacteria, mold, or fungal growth in dry powder form. Microbial growth may occur in mucilages of the polymer solution. Although the gel properties are not affected by such growth, this phenomenon is usually unacceptable. The addition of appropriate preservatives prevents mold and bacterial growth in these mucilages. Exposure of polycarbophil mucilages to high temperatures results in a drop in viscosity.

Polycarbophil polymers are very hygroscopic and should be packed in air-tight, corrosion-resistant containers. They should be stored in a cool, dry place, and the container should be kept closed when not in use. Moisture pickup does not affect the efficiency of the resins, but resin containing high levels of moisture is more difficult to disperse and weigh accurately. Glass, plastic, or resin-lined containers are recommended for products containing polycarbophil. Packaging in aluminum tubes usually requires formulations to have a pH less than 6.5, and packaging in other metallic tubes or containers necessitates a pH greater than 7.7 to prolong polycarbophil stability.

12 Incompatibilities

Heat may be generated if polycarbophil comes into contact with strong basic materials such as ammonia, sodium hydroxide, potassium hydroxide, or strongly basic amines. Polycarbophil polymers are not compatible with cationic polymers, strong acids, and high levels of electrolytes, as electrolytes tend to reduce the viscosity of polycarbophil-based gels.

13 Method of Manufacture

Polycarbophils are synthetic, high-molecular-weight, crosslinked polymers of acrylic acid. These poly(acrylic acid) polymers are crosslinked with divinyl glycol. They are synthesized via precipitation polymerization in ethyl acetate and then dried.

14 Safety

Polycarbophil polymers have a long history of safe and effective use in topical gels, creams, lotions, and ointments. They have been shown to have extremely low irritancy properties and are nonsensitizing with repeated usage.

The use of these polymers is supported by extensive toxicological studies.(30)

LD_{50} (guinea pig, oral): 2.0 g/kg
LD_{50} (mouse, IP): 0.039 g/kg
LD_{50} (mouse, IV): 0.070 g/kg
LD_{50} (mouse, oral): 4.6 g/kg
LD_{50} (rat, oral): >2.5 g/kg
LD_{50} (rabbit, skin): >3.0 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Excessive dust generation should be minimized to avoid the risk of explosion (lowest explosive concentration is 130 g/m^3). Polycarbophil dust is an irritant to eyes, mucous membranes, and the respiratory tract. Powder/dust eye irritation is a physical, not a chemical effect. Solid particles on the eye (powder/dust) may cause pain and be accompanied by irritation. Saline should be used for irrigation purposes. Dust inhalation may cause coughing, mucus production, and shortness of breath. Contact dermatitis may occur in individuals under extreme conditions of prolonged and repeated contact, high exposure, high temperature, and occlusion (being held onto the skin) by clothing. Gloves, eye protection, and a dust respirator are recommended during handling. Polycarbophil should be used in well-ventilated conditions.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (vaginal gel; oral, troche). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Calcium polycarbophil; carbomer.

Calcium polycarbophil

Empirical formula: calcium polycarbophil is the calcium salt of polyacrylic acid crosslinked with divinyl glycol.

Molecular weight: the molecular weight of these polymers is theoretically estimated to range from 700 000 to 3–4 billion. There are, however, no methods currently available to measure the actual molecular weight of a crosslinked (i.e. three-dimensional) polymer of this type.

CAS number: [9003-97-8]

Synonyms: *Noveon CA-1*; *Noveon CA-2*.

Appearance: white powder with slightly acetic odor.

Acidity/alkalinity: pH = 6.0–8.0 (1% w/v aqueous dispersion).

Density (bulk): 0.86 g/cm^3 (*Noveon CA-1*); 0.55 g/cm^3 (*Noveon CA-2*).

Moisture content: <10%

Pharmacopeial specifications: *see* Table II.

Comments: *Noveon CA-1* is a coarsely ground grade of calcium polycarbophil and is ideally suited for formulating swallowable bulk laxative tablets, while *Noveon CA-2* is a finely ground grade and is designed for formulating chewable or swallowable bulk laxative tablets. Both grades swell in the intestinal tract, taking advantage of the natural

Table II: Pharmacopeial specifications for calcium polycarbophil.

Test	USP 28
Identification	+
Loss on drying	⩽10%
Absorbing power	⩾35 g/g
Organic volatile impurities	+
Calcium content (on dried basis)	18–22%

water absorbency of polycarbophil. The swollen polycarbophil gel then acts as a bulk laxative as it moves through the gastrointestinal tract.

18 Comments

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21 Authors

KK Singh.

22 Date of Revision

25 August 2005.

Polydextrose

1 Nonproprietary Names

None adopted.

2 Synonyms

E1200; *Litesse*; polydextrose A; polydextrose K.

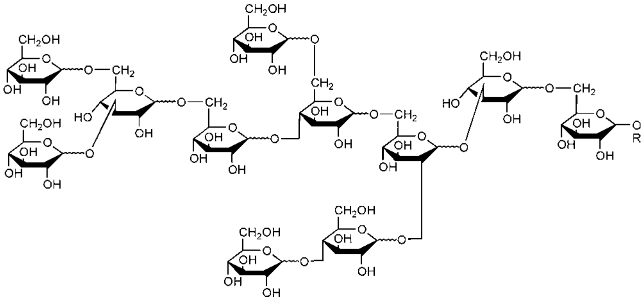
3 Chemical Name and CAS Registry Number

Polydextrose [68424-04-4]

4 Empirical Formula and Molecular Weight

$(C_6H_{12}O_6)_x$ 1200–2000 (average)

5 Structural Formula



See Section 18.

6 Functional Category

Base for medicated confectionery; coating agent; granulation aid; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Polydextrose is used in pharmaceutical formulations and food products. In food products it is used as a bulking agent; it also has texturizing and humectant properties.

Although polydextrose can be used in a wide range of pharmaceutical formulations, its primary use is in solid-dosage forms.

In tableting, polydextrose solutions are used as binders in wet-granulation processes. Polydextrose is also used in the manufacture of directly compressible tableting excipients. Polydextrose solutions may also be used, in conjunction with other materials, as a film and tablet coating agent.

Polydextrose acts as a bulking agent in the formulation of 'sugar-free' confectionery-type dosage forms. In conjunction with isomalt, lactitol, or maltitol, polydextrose can be used in the manufacture of 'sugar-free' hard-boiled candies and acacia lozenges or pastilles.

The combination of high water solubility and high viscosity of polydextrose facilitates the processing of sugar-free candies of excellent quality. Polydextrose is amorphous and does not crystallize at low temperatures or high concentrations, so it can be used to control the crystallization of polyols and sugars and therefore the structure and texture of the final product.

8 Description

Polydextrose occurs as an odorless, off-white to light tan powder with a bland, slightly tart taste.

9 Pharmacopeial Specifications

See Section 18.

10 Typical Properties

Acidity/alkalinity: pH = 2.5 minimum (10% w/v aqueous solution)

Density (bulk): 0.625 g/cm^3

Density (tapped): 0.694 g/cm^3

Heat of solution: 8 kcal/g

Melting point: polydextrose is an amorphous polymer that does not have a melting range. However, it can undergo a viscosity transition at a temperature as low as 150–160°C.

Moisture content: at relative humidities above approximately 60%, polydextrose absorbs significant amounts of moisture; *see* Section 11. *See also* Figure 1.

Refractive index: n_D^{20}= 1.3477 (10% w/v aqueous solution)

Solubility: completely miscible in water. Sparingly soluble to insoluble in most organic solvents. Polydextrose has a higher water solubility than most carbohydrates and polyols, allowing the preparation of 80% w/v solutions at 20°C. Polydextrose is soluble in ethanol and only partially soluble in glycerin and propylene glycol.

Viscosity (dynamic): polydextrose solutions behave as Newtonian fluids. Polydextrose has a higher viscosity than sucrose or sorbitol at equivalent temperatures. This characteristic enables polydextrose to provide the desirable mouthfeel and textural qualities that are important when formulating syrups and viscous solutions. *See* Figure 2.

11 Stability and Storage Conditions

Polydextrose is hygroscopic and absorbs significant amounts of moisture at relative humidities greater than 60%. Under dry storage conditions it has good stability.

The bulk material should be stored in a cool, dry place in well-closed containers.

12 Incompatibilities

Incompatible with oxidizing agents, strong acids, and alkalis, forming a brown coloration and depolymerizing.

13 Method of Manufacture

Dextrose and sorbitol undergo a catalytic condensation reaction with an acid. Further purification may be performed to

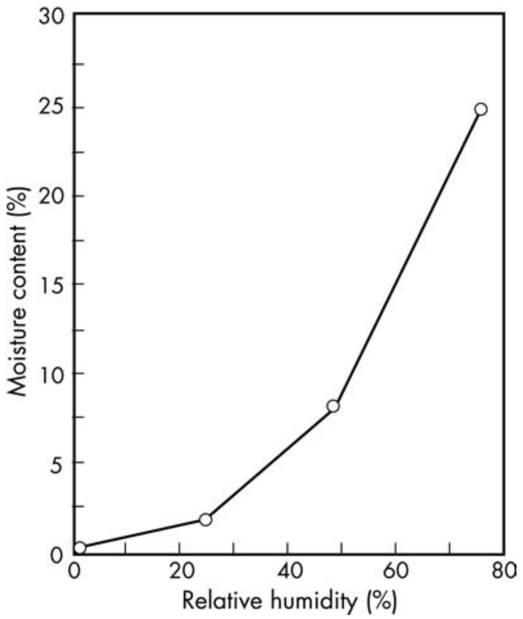


Figure 1: Moisture content of polydextrose at 20°C.

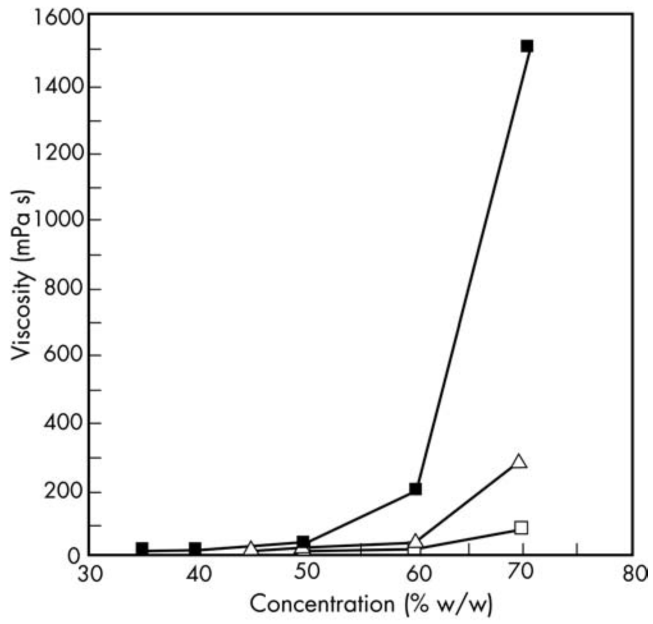


Figure 2: Viscosity of polydextrose solutions at 25°C at various concentrations.
△: Sucrose
■: Polydextrose
□: Sorbitol

remove acidity and flavor notes generated during the condensation.

14 Safety

Polydextrose is used in oral pharmaceutical applications, food products, and confectionery and is generally regarded as a relatively nontoxic and nonirritant material.(1,2)

However, excessive consumption of non-digestible carbohydrates, such as polydextrose, can lead to gastrointestinal distress. After evaluating a series of clinical studies, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the European Commission Scientific Committee for Food (EC/SCF) concluded that polydextrose was better tolerated than other digestible carbohydrates such as polyols. The committee concluded that polydextrose has a mean laxative threshold of approximately 90 g/day (1.3 g/kg body-weight) or 50 g as a single dose.(3) *See also* Section 18.

LD$_{50}$ (mouse, oral): >30 g/kg
LD$_{50}$ (rat, oral): >15 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Polydextrose may be irritant to the eyes. Eye protection and gloves are recommended. Conventional dust-control practices should be employed.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral tablets). Included in non-parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Dextrose.

18 Comments

Polydextrose is a randomly bonded polymer prepared by the condensation of a melt that consists of approximately 90% w/w D-glucose, 10% w/w sorbitol, and 1% w/w citric acid or 0.1% w/w phosphoric acid.

The 1,6 glycosidic linkage predominates in the polymer, but other possible bonds are present. The product contains small quantities of free glucose, sorbitol, and D-anhydroglucoses (levoglucosan), with traces of citric or phosphoric acid.

Polydextrose may be partially reduced by transition-metal catalytic hydrogenation in aqueous solution. It may be neutralized with any food-grade base and/or decolorized and deionized for further purification.

Although not currently included in any pharmacopeias, a specification for polydextrose is contained in the Food Chemicals Codex (FCC). *See* Table I.

Polydextrose is partially fermented by intestinal microorganisms to produce volatile fatty acids. The volatile fatty acids are absorbed in the large intestine. Because of the inefficient way the human body derives energy from volatile fatty acids, polydextrose contributes only one-quarter of the energy of the equivalent weight of sugar, i.e, ≈4 kJ/g (1 kcal/g).(4–6)

When consumed, polydextrose has a negligible effect on blood glucose levels. Polydextrose is metabolized independently of insulin and contributes only one quarter of the energy of normal carbohydrate.

A specification for polydextrose is contained in the Food Chemicals Codex (FCC).

Table I: Food Chemicals Codex specifications for polydextrose.[3]

Test	FCC 1996 (Suppl. 2)
Identification	+
Heavy metals	$\leqslant$5 ppm
5-Hydroxymethylfurfural	$\leqslant$0.1%
Lead	$\leqslant$0.5 ppm
Molecular weight limit	+
Monomers	
1,6-Anhydro-D-glucose	$\leqslant$4.0%
Glucose and sorbitol	$\leqslant$6.0%
pH of a 10% solution	
Untreated	2.5–7.0
Neutralized	5.0–6.0
Residue on ignition	
Untreated	$\leqslant$0.3%
Neutralized	$\leqslant$2.0%
Water	$\leqslant$4.0%
Assay	$\geqslant$90.0%

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21 Authors

PJ Weller.

22 Date of Revision

19 April 2005.

Polyethylene Glycol

1 Nonproprietary Names

BP:	Macrogols
JP:	Macrogol 400 Macrogol 1500 Macrogol 4000 Macrogol 6000 Macrogol 20000
PhEur:	Macrogola
USPNF:	Polyethylene glycol

2 Synonyms

Carbowax; *Carbowax Sentry*; *Lipoxol*; *Lutrol E*; PEG; *Pluriol E*; polyoxyethylene glycol.

3 Chemical Name and CAS Registry Number

α-Hydro-ω-hydroxypoly(oxy-1,2-ethanediyl) [25322-68-3]

4 Empirical Formula and Molecular Weight

$HOCH_2(CH_2OCH_2)_mCH_2OH$ where *m* represents the average number of oxyethylene groups.

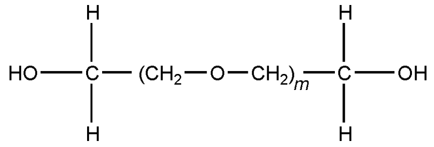
Alternatively, the general formula $H(OCH_2CH_2)_nOH$ may be used to represent polyethylene glycol, where *n* is a number *m* in the previous formula + 1.

See Table I for the average molecular weights of typical polyethylene glycols. Note that the number that follows PEG indicates the average molecular weight of the polymer.

Table I: Structural formula and molecular weight of typical polyethylene glycol polymers.

Grade	*m*	Average molecular weight
PEG 200	4.2	190–210
PEG 300	6.4	285–315
PEG 400	8.7	380–420
PEG 540 (blend)	—	500–600
PEG 600	13.2	570–613
PEG 900	15.3	855–900
PEG 1000	22.3	950–1 050
PEG 1450	32.5	1 300–1 600
PEG 1540	28.0–36.0	1 300–1 600
PEG 2000	40.0–50.0	1 800–2 200
PEG 3000	60.0–75.0	2 700–3 300
PEG 3350	75.7	3 000–3 700
PEG 4000	69.0–84.0	3 000–4 800
PEG 4600	104.1	4 400–4 800
PEG 8000	181.4	7 000–9 000

5 Structural Formula



$$HO-CH_2-(CH_2-O-CH_2)_m-CH_2-OH$$

6 Functional Category

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations. It has been used experimentally in biodegradable polymeric matrices used in controlled-release systems.(1)

Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin; *see* Section 14. They do not readily penetrate the skin, although the polyethylene glycols are water-soluble and are easily removed from the skin by washing, making them useful as ointment bases.(2) Solid grades are generally employed in topical ointments, with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol.

Mixtures of polyethylene glycols can be used as suppository bases,(3) for which they have many advantages over fats. For example, the melting point of the suppository can be made higher to withstand exposure to warmer climates; release of the drug is not dependent upon melting point; the physical stability on storage is better; and suppositories are readily miscible with rectal fluids. Polyethylene glycols have the following disadvantages: they are chemically more reactive than fats; greater care is needed in processing to avoid inelegant contraction holes in the suppositories; the rate of release of water-soluble medications decreases with the increasing molecular weight of the polyethylene glycol; and polyethylene glycols tend to be more irritating to mucous membranes than fats.

Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, polyethylene glycols can act as emulsion stabilizers.

Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. However, they may cause hardening of the capsule shell by preferential absorption of moisture from gelatin in the shell.

In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms.

In solid-dosage formulations, higher-molecular-weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules.(4) However, they have only limited binding action when used alone, and can prolong disintegration if present in concentrations greater than 5%

w/w. When used for thermoplastic granulations,(5–7) a mixture of the powdered constituents with 10–15% w/w PEG 6000 is heated to 70–75°C. The mass becomes pastelike and forms granules if stirred while cooling. This technique is useful for the preparation of dosage forms such as lozenges when prolonged disintegration is required.

Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol.(8) Animal studies have also been performed using polyethylene glycols as solvents for steroids in osmotic pumps.

In film coatings, solid grades of polyethylene glycol can be used alone for the film-coating of tablets or can be useful as hydrophilic polishing materials. Solid grades are also widely used as plasticizers in conjunction with film-forming polymers.(9) The presence of polyethylene glycols in film coats, especially of liquid grades, tends to increase their water permeability and may reduce protection against low pH in enteric-coating films. Polyethylene glycols are useful as plasticizers in microencapsulated products to avoid rupture of the coating film when the microcapsules are compressed into tablets.

Polyethylene glycol grades with molecular weights of 6000 and above can be used as lubricants, particularly for soluble tablets. The lubricant action is not as good as that of magnesium stearate, and stickiness may develop if the material becomes too warm during compression. An antiadherent effect is also exerted, again subject to the avoidance of overheating.

Polyethylene glycols have been used in the preparation of urethane hydrogels, which are used as controlled-release agents. It has also been used in insulin-loaded microparticles for the oral delivery of insulin;(10,11) it has been used in inhalation preparations to improve aerosolization;(12) polyethylene glycol nanoparticles have been used to improve the oral bioavailability of cyclosporine;(13) it has been used in self-assembled polymeric nanoparticles as a drug carrier;(14) and copolymer networks of polyethylene glycol grafted with poly(methacrylic acid) have been used as bioadhesive controlled drug delivery formulations.(15)

8 Description

The USPNF 23 describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200–600 are liquids; grades 1000 and above are solids at ambient temperatures.

Liquid grades (PEG 200–600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures.

Solid grades (PEG>1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free-flowing milled powders.

9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Density:
1.11–1.14 g/cm^3 at 25°C for liquid PEGs;
1.15–1.21 g/cm^3 at 25°C for solid PEGs.

Flash point:
182°C for PEG 200;
213°C for PEG 300;
238°C for PEG 400;
250°C for PEG 600.

Freezing point:
<-65°C PEG 200 sets to a glass;
-15 to -8°C for PEG 300;
4–8°C for PEG 400;
15–25°C for PEG 600.

Melting point:
37–40°C for PEG 1000;
44–48°C for PEG 1500;
40–48°C for PEG 1540;
45–50°C for PEG 2000;
48–54°C for PEG 3000;
50–58°C for PEG 4000;
55–63°C for PEG 6000;
60–63°C for PEG 8000;
60–63°C for PEG 20000.

Moisture content: liquid polyethylene glycols are very hygroscopic, although hygroscopicity decreases with increasing molecular weight. Solid grades, e.g. PEG 4000 and above, are not hygroscopic. *See* Figures 1, 2 and 3.

Particle size distribution: *see* Figures 4 and 5.

Refractive index:
n_D^{25} = 1.459 for PEG 200;
n_D^{25} = 1.463 for PEG 300;
n_D^{25} = 1.465 for PEG 400;
n_D^{25} = 1.467 for PEG 600.

Solubility: all grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher-molecular-weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%),

Table II: Pharmacopeial specifications for polyethylene glycol.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	—
Characters	—	+	—
Acidity or alkalinity	—	+	—
Appearance of solution	—	+	+
Density	—	*See* Table IV	—
Freezing point	*See* Table III	*See* Table IV	—
Viscosity	—	*See* Table IV	*See* Table V
Average molecular weight	*See* Table III	—	*See* Table V
pH (5% w/v solution)	*See* Table III	—	4.5–7.5
Hydroxyl value	—	*See* Table IV	—
Reducing substances	—	+	—
Residue on ignition	*See* Table III	—	⩽0.1%
Sulfated ash	—	⩽0.2%	—
Limit of ethylene glycol and diethylene glycol	⩽0.25%	⩽0.4%	⩽0.25%
Ethylene oxide	—	⩽1 ppm	⩽10 μg/g
1,4-Dioxane	—	⩽10 ppm	⩽10 μg/g
Heavy metals	—	⩽20 ppm	⩽5 μg/g
Organic volatile impurities	—	—	+
Water	⩽1.0%	⩽2.0%	—
Formaldehyde	—	⩽15 ppm	—

Table III: Specifications from JP 2001.

Type of PEG	Average molecular weight	Freezing point (°C)	pH (5% w/v solution)	Residue on ignition
400	380–420	4–8	4.0–7.0	⩽0.1%
1500	—	37–41	4.0–7.0	⩽0.1%
4000	2 600–3 800	53–57	4.0–7.5	⩽0.25%
6000	7 300–9 300	56–61	4.5–7.5	⩽0.25%
20000	15 000–25 000	56–64	4.5–7.5	⩽0.25%

and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

Surface tension: approximately 44 mN/m (44 dynes/cm) for liquid polyethylene glycols; approximately 55 mN/m (55 dynes/cm) for 10% w/v aqueous solution of solid polyethylene glycol.

Viscosity (kinematic): *see* Tables IV, V, and VI.

11 Stability and Storage Conditions

Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid.

Polyethylene glycols and aqueous polyethylene glycol solutions can be sterilized by autoclaving, filtration, or gamma irradiation.(16) Sterilization of solid grades by dry heat at 150°C for 1 hour may induce oxidation, darkening, and the formation of acidic degradation products. Ideally, sterilization should be carried out in an inert atmosphere. Oxidation of polyethylene glycols may also be inhibited by the inclusion of a suitable antioxidant.

If heated tanks are used to maintain normally solid polyethylene glycols in a molten state, care must be taken to avoid contamination with iron, which can lead to discoloration. The temperature must be kept to the minimum necessary to ensure fluidity; oxidation may occur if polyethylene glycols are exposed for long periods to temperatures exceeding 50°C. However, storage under nitrogen reduces the possibility of oxidation.

Polyethylene glycols should be stored in well-closed containers in a cool, dry place. Stainless steel, aluminum, glass, or lined steel containers are preferred for the storage of liquid grades.

12 Incompatibilities

The chemical reactivity of polyethylene glycols is mainly confined to the two terminal hydroxyl groups, which can be either esterified or etherified. However, all grades can exhibit some oxidizing activity owing to the presence of peroxide impurities and secondary products formed by autoxidation.

Liquid and solid polyethylene glycol grades may be incompatible with some coloring agents.

The antibacterial activity of certain antibiotics is reduced in polyethylene glycol bases, particularly that of penicillin and bacitracin. The preservative efficacy of the parabens may also be impaired owing to binding with polyethylene glycols.

Physical effects caused by polyethylene glycol bases include softening and liquefaction in mixtures with phenol, tannic acid, and salicylic acid. Discoloration of sulfonamides and dithranol can also occur and sorbitol may be precipitated from mixtures. Plastics, such as polyethylene, phenolformaldehyde, polyvinyl chloride, and cellulose-ester membranes (in filters) may be softened or dissolved by polyethylene glycols. Migration of polyethylene glycol can occur from tablet film coatings, leading to interaction with core components.

13 Method of Manufacture

Polyethylene glycols are condensation polymers formed by the reaction of ethylene oxide and water under pressure in the presence of a catalyst.

14 Safety

Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials.(17–19)

Adverse reactions to polyethylene glycols have been reported, the greatest toxicity being with glycols of low molecular weight. However, the toxicity of glycols is relatively low.

Polyethylene glycols administered topically may cause stinging, especially when applied to mucous membranes. Hypersensitivity reactions to polyethylene glycols applied topically have also been reported, including urticaria and delayed allergic reactions.(20)

The most serious adverse effects associated with polyethylene glycols are hyperosmolarity, metabolic acidosis, and renal failure following the topical use of polyethylene glycols in burn patients.(21) Topical preparations containing polyethylene glycols should therefore be used cautiously in patients with renal failure, extensive burns, or open wounds.

Table IV: Specifications from PhEur 2005.

Type of PEG	Density (g/cm^3)	Freezing point (°C)	Hydroxyl value	Viscosity (dynamic) [mPa s (cP)]	Viscosity (kinematic) [mm^2/s (cSt)]
300	1.120	—	340–394	80–105	71–94
400	1.120	—	264–300	105–130	94–116
600	1.080	15–25	178–197	15–20	13.9–18.5
1000	1.080	35–40	107–118	22–30	20.4–27.7
1500	1.080	42–48	70–80	34–50	31–46
3000	1.080	50–56	34–42	75–100	69–93
3350	1.080	53–57	30–38	83–120	76–110
4000	1.080	53–59	25–32	110–170	102–158
6000	1.080	55–61	16–22	200–270	185–250
8000	1.080	55–62	12–16	260–510	240–472
20000	1.080	⩾57	—	2 700–3 500	2 500–3 200
35000	1.080	⩾57	—	11 000–14 000	10 000–13 000

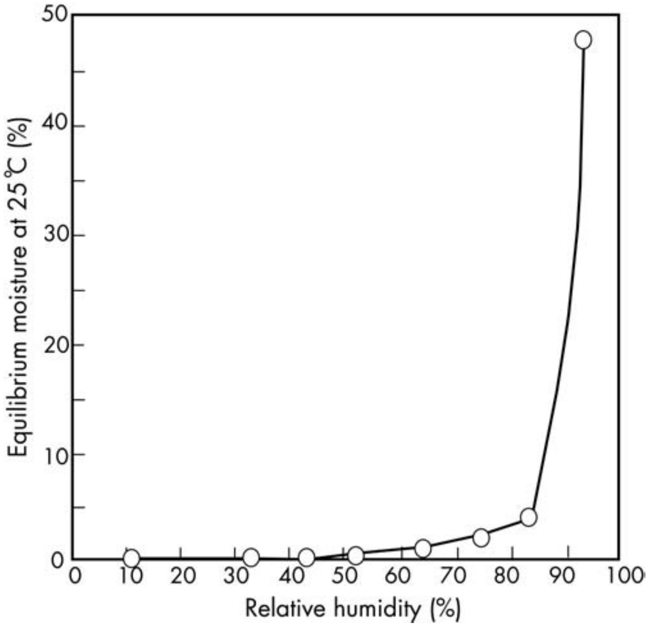


Figure 1: Equilibrium moisture content of PEG 4000 (McKesson, Lot No. B192–8209) at 25°C.

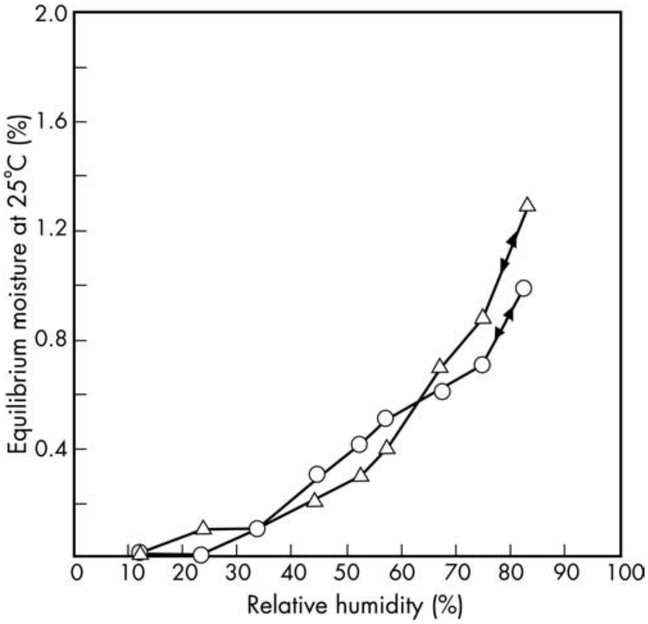


Figure 3: Equilibrium moisture content of PEG 6000 at 25°C.
○: PEG 6000 powder (Union Carbide Corp., Lot no. B–507)
△: PEG E–6000 (BASF, Lot no. WPNA–124B)

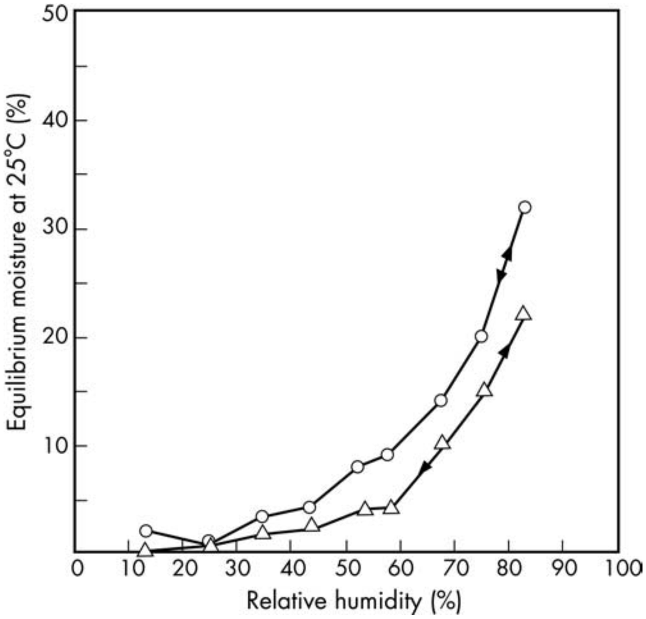


Figure 2: Equilibrium moisture content of PEG 4000 at 25°C.
○: PEG 4000 powder (Union Carbide Corp, Lot no. B-251)
△: PEG E–4000 (BASF, Lot no. WPYA–575B)

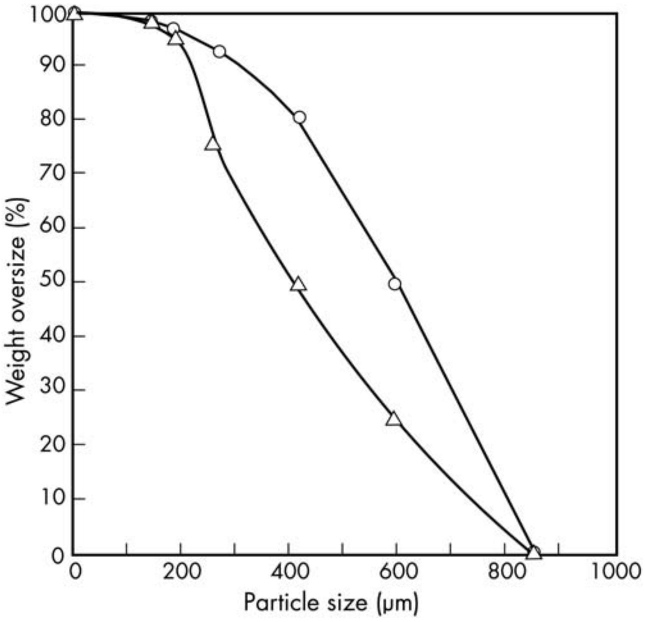


Figure 4: Particle size distribution of PEG 4000 and PEG 6000 flakes.
○: PEG 4000 flakes
△: PEG 6000 flakes

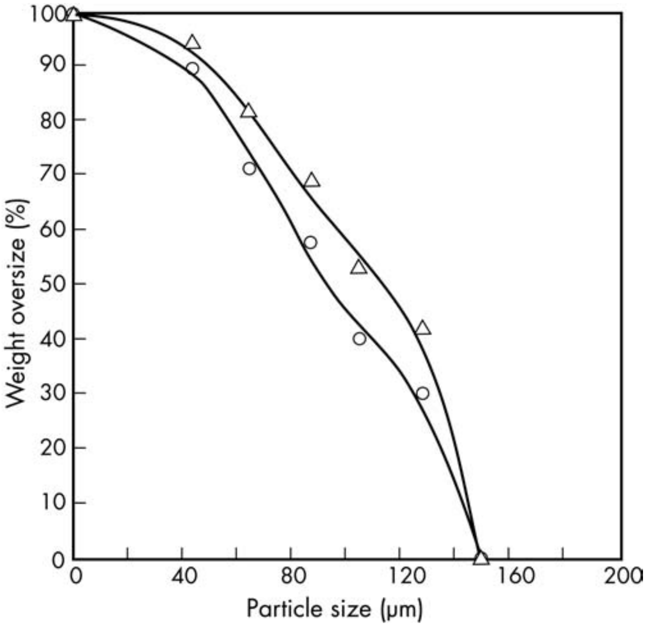


Figure 5: Particle size distribution of PEG 4000 and PEG 6000 powder.
○: PEG 4000 powder
△: PEG 6000 powder

Oral administration of large quantities of polyethylene glycols can have a laxative effect. Therapeutically, up to 4 L of an aqueous mixture of electrolytes and high-molecular-weight polyethylene glycol is consumed by patients undergoing bowel cleansing.(22)

Liquid polyethylene glycols may be absorbed when taken orally, but the higher-molecular-weight polyethylene glycols are not significantly absorbed from the gastrointestinal tract. Absorbed polyethylene glycol is excreted largely unchanged in the urine, although polyethylene glycols of low molecular weight may be partially metabolized.

The WHO has set an estimated acceptable daily intake of polyethylene glycols at up to 10 mg/kg body-weight.(23)

In parenteral products, the maximum recommended concentration of PEG 300 is approximately 30% v/v as hemolytic effects have been observed at concentrations greater than about 40% v/v.

For animal toxicity data, *see* Table VII.(24)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (dental preparations; IM and IV injections; ophthalmic preparations; oral capsules, solutions, syrups, and tablets; rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

Table V: Specification for viscosity of polyethylene glycol of the given nominal molecular weight at 98.9°C ± 0.3°C from the USPNF 23.

Type of PEG (nominal average molecular weight)	Viscosity (kinematic) [mm^2/s (cSt)]
200	3.9–4.8
300	5.4–6.4
400	6.8–8.0
500	8.3–9.6
600	9.9–11.3
700	11.5–13.0
800	12.5–14.5
900	15.0–17.0
1000	16.0–19.0
1100	18.0–22.0
1200	20.0–24.5
1300	22.0–27.5
1400	24–30
1450	25–32
1500	26–33
1600	28–36
1700	31–39
1800	33–42
1900	35–45
2000	38–49
2100	40–53
2200	43–56
2300	46–60
2400	49–65
2500	51–70
2600	54–74
2700	57–78
2800	60–83
2900	64–88
3000	67–93
3250	73–105
3350	76–110
3500	87–123
3750	99–140
4000	110–158
4250	123–177
4500	140–200
4750	155–228
5000	170–250
5500	206–315
6000	250–390
6500	295–480
7000	350–590
7500	405–735
8000	470–900

Table VI: Viscosity of selected polyethylene glycols at 25°C and 99°C.

Type of PEG	Viscosity [mm^2/s (cSt)]	
	25°C	**99°C**
PEG 200	39.9	4.4
PEG 300	68.8	5.9
PEG 400	90.0	7.4
PEG 600	131	11.0
PEG 1000 solid	19.5	—
PEG 2000 solid	47	—
PEG 4000 solid	180	—
PEG 6000 solid	580	—
PEG 20000 solid	6 900	—

Table VII: Animal toxicity data (LD$_{50}$) for various grades of polyethylene glycol.[24]

PEG grade	LD$_{50}$ (g/kg)								
	Guinea pig (oral)	Mouse (IP)	Mouse (IV)	Mouse (oral)	Rabbit (oral)	Rabbit (IV)	Rat (IP)	Rat (IV)	Rat (oral)
PEG 200	—	7.5	—	34	19.9	—	—	—	28.0
PEG 300	19.6	—	—	—	17.3	—	—	—	27.5
PEG 400	15.7	10.0	8.6	28.9	26.8	—	9.7	7.3	—
PEG 600	—	—	—	47	—	—	—	—	38.1
PEG 1000	—	20	—	—	—	—	15.6	—	32
PEG 1500	28.9	—	—	—	28.9	8	17.7	—	44.2
PEG 4000	50.9	—	16	—	76	—	11.6	—	50
PEG 6000	50	—	—	—	—	—	6.8	—	—

17 Related Substances

Polyoxyethylene alkyl ethers; polyethylene oxide; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene stearates; suppository bases.

18 Comments

A specification for polyethylene glycol is contained in the Food Chemicals Codex (FCC).

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21 Authors

JC Price.

22 Date of Revision

29 August 2005.

Polyethylene Oxide

1 Nonproprietary Names

USPNF: Polyethylene oxide

2 Synonyms

Polyox; polyoxirane; polyoxyethylene.

3 Chemical Name and CAS Registry Number

Polyethylene oxide [25322-68-3]

4 Empirical Formula and Molecular Weight

See Table I.

5 Structural Formula

The USPNF 23 describes polyethylene oxide as a nonionic homopolymer of ethylene oxide, represented by the formula $(CH_2CH_2O)_n$, where n represents the average number of oxyethylene groups. It may contain up to 3% of silicon dioxide.

6 Functional Category

Mucoadhesive; tablet binder; thickening agent.

7 Applications in Pharmaceutical Formulation or Technology

Polyethylene oxide can be used as a tablet binder at concentrations of 5–85%. The higher molecular weight grades provide delayed drug release via the hydrophilic matrix approach; *see* Table I.

The relationship between swelling capacity and molecular weight is a good guide when selecting products for use in immediate- or sustained-release matrix formulations; *see* Figure 1.

Polyethylene oxide has been shown to be an excellent mucoadhesive polymer.(1) Low levels of polyethylene oxide are effective thickeners, although alcohol is usually added to water-based formulations to provide improved viscosity stability; *see* Table II. Polyethylene oxide films demonstrate good lubricity when wet. This property has been utilized in the development of coatings for medical devices. Polyethylene oxide can be radiation crosslinked in solution to produce a hydrogel that can be used in wound care applications.

8 Description

White to off-white, free-flowing powder. Slight ammoniacal odor.

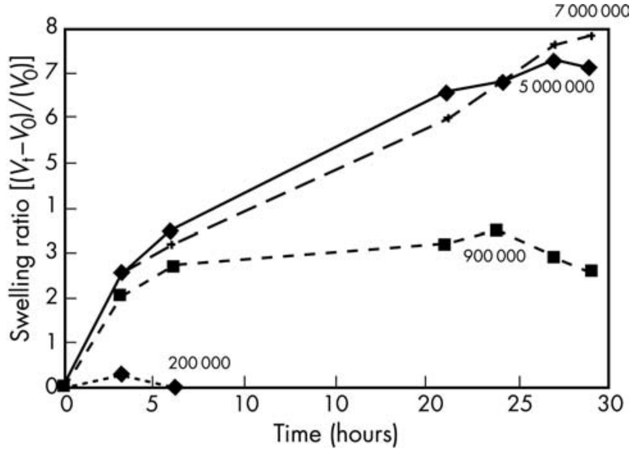

Figure 1: Swelling capacity of polyethylene oxide (Polyox WSR). Measured for four molecular weight grades; 28 mm tablets in 300 mL of water.

Table I: Number of repeat units and molecular weight as a function of polymer grade for polyethylene oxide.

Polyox grade	Approximate number of repeating units	Approximate molecular weight
WSR *N*-10	2 275	100 000
WSR *N*-80	4 500	200 000
WSR *N*-750	6 800	300 000
WSR *N*-3000	9 100	400 000
WSR 205	14 000	600 000
WSR 1105	20 000	900 000
WSR *N*-12K	23 000	1 000 000
WSR *N*-60K	45 000	2 000 000
WSR 301	90 000	4 000 000
WSR Coagulant	114 000	5 000 000
WSR 303	159 000	7 000 000

Note: molecular weight based on dilute viscosity measurements.

Table II: Polyethylene oxide viscosity at 25°C (mPa s).

Polyox grade	5% solution	2% solution	1% solution
WSR *N*-10	30–50	—	—
WSR *N*-80	55–90	—	—
WSR *N*-750	600–1 200	—	—
WSR *N*-3000	2 250–4 500	—	—
WSR 205	4 500–8 800	—	—
WSR 1105	8 800–17 600	—	—
WSR *N*-12K	—	400–800	—
WSR *N*-60K	—	2 000–4 000	—
WSR 301	—	—	1 650–5 500
WSR coagulant	—	—	5 500–7 500
WSR 303	—	—	7 500–10 000

Note: all solution concentrations are based on the water content of the hydro-alcoholic solutions.

9 Pharmacopeial Specifications

See Table III.

Table III: Pharmacopeial specifications for polyethylene oxide.

Test	USPNF 23
Identification	+
Loss on drying	⩽1.0%
Silicon dioxide and nonsilicon dioxide residue on ignition	⩽2.0%
Silicon dioxide	⩽3.0%
Heavy metals	⩽0.001%
Free ethylene oxide	⩽0.001%
Organic volatile impurities	+
Viscosity	+

10 Typical Properties

Angle of repose: 34°
Density (true): 1.3 g/cm^3
Melting point: 65–70°C
Moisture content: <1%
Solubility: polyethylene oxide is soluble in water and a number of common organic solvents such as acetonitrile, chloroform, and methylene chloride. It is insoluble in aliphatic hydrocarbons, ethylene glycol, and most alcohols.(2)
Viscosity (dynamic): *see* Table II.

11 Stability and Storage Conditions

Store in tightly sealed containers in a cool, dry place. Avoid exposure to high temperatures since this can result in reduction in viscosity.

12 Incompatibilities

Polyethylene oxide is incompatible with strong oxidizing agents.

13 Method of Manufacture

Polyethylene oxide is prepared by the polymerization of ethylene oxide using a suitable catalyst.(1)

14 Safety

Animal studies suggest that polyethylene oxide has a low level of toxicity regardless of the route of administration. It is poorly absorbed from the gastrointestinal tract but appears to be completely and rapidly eliminated. The resins are neither skin irritants nor sensitizers, and they do not cause eye irritation.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (sustained-release tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Polyethylene glycol.

18 Comments

—

19 Specific References

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21 Authors

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22 Date of Revision

17 August 2005.

Polymethacrylates

1 Nonproprietary Names

BP: Methacrylic acid–ethyl acrylate copolymer (1 : 1)
PhEur: Acidum methacrylicum et ethylis acrylas polymerisatum 1 : 1
Acidum methacrylicum et ethylis acrylas polymerisatum 1 : 1 dispersio 30 per centum
Acidum methacrylicum et methylis methacrylas polymerisatum 1 : 1
Acidum methacrylicum et methylis methacrylas polymerisatum 1 : 2
Copolymerum methacrylatis butylati basicum
Polyacrylatis dispersion 30 per centum
USPNF: Ammonio methacrylate copolymer
Methacrylic acid copolymer
Methacrylic acid copolymer dispersion

Note that three separate monographs applicable to polymethacrylates are contained in the USPNF 23; *see* Section 9. Several different types of material are defined in the monographs. The PhEur 2005 contains four separate monographs applicable to polymethacrylates.

2 Synonyms

Acryl-EZE; *Acryl-EZE MP*; *Eastacryl 30D*; *Eudragit*; *Kollicoat MAE 30 D*; *Kollicoat MAE 30 DP*; polymeric methacrylates. *See also* Table I.

3 Chemical Name and CAS Registry Number

See Table I.

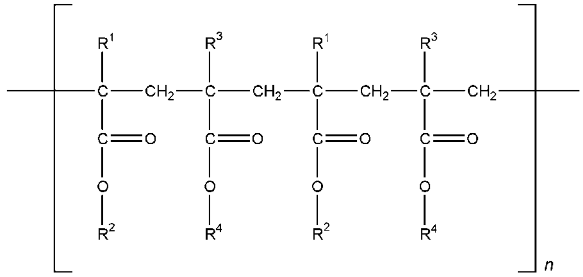
4 Empirical Formula and Molecular Weight

The PhEur 2005 describes methacrylic acid–ethyl acrylate copolymer (1 : 1) as a copolymer of methacrylic acid and ethyl acrylate having a mean relative molecular mass of about 250 000. The ratio of carboxylic groups to ester groups is about 1 : 1. It may contain suitable surfactants such as sodium dodecyl sulfate or polysorbate 80. An aqueous 30% w/v dispersion of this material is also defined in a separate monograph. Methacrylic acid–methyl methacrylate copolymer (1 : 1) is described in the PhEur 2005 as a copolymer of methacrylic acid and methyl methacrylate having a mean relative molecular mass of about 135 000. The ratio of carboxylic acid to ester groups is about 1 : 1. A further monograph in the PhEur 2005 describes methacrylic acid–methyl methacrylate copolymer (1 : 2), where the ratio of carboxylic acid to ester groups is about 1 : 2. The PhEur 2005 describes basic butylated methyacrylate copolymer as a copolymer of (2-dimethylaminoethyl) methacrylate, butyl methyacrylate, and methyl methacrylate having a mean relative molecular mass of about 150 000. The ratio of (2-dimethylaminoethyl) methacrylate groups to butyl methyacrylate and methyl methacrylate groups is about 2 : 1 : 1. Polyacrylate dispersion (30 per cent) is described in the PhEur 2005 as a dispersion in water of a copolymer of ethyl acrylate and methyl methacrylate having a mean relative molecular mass of about 800 000. It may contain a suitable emulsifier.

The USPNF 23 describes methacrylic acid copolymer as a fully polymerized copolymer of methacrylic acid and an acrylic or methacrylic ester. Three types of copolymers, namely Type A, Type B, and Type C, are defined in the monograph. They vary in their methacrylic acid content and solution viscosity. Type C may contain suitable surface-active agents. Two additional polymers, Type A (*Eudragit RL*) and Type B (*Eudragit RS*), also referred to as ammonio methacrylate copolymers, consisting of fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups, are also described in the USPNF 23. A further monograph for an aqueous dispersion of Type C methacrylic acid copolymer is also defined; *see* Section 9.

Typically, the molecular weight of the polymer is ⩾100 000.

5 Structural Formula



For *Eudragit E*:
R^1, R^3 = CH_3
R^2 = $CH_2CH_2N(CH_3)_2$
R^4 = CH_3, C_4H_9
For *Eudragit L* and *Eudragit S*:
R^1, R^3 = CH_3
R^2 = H
R^4 = CH_3
For *Eudragit FS*:
R^1 = H
R^2 = H, CH_3
R^3 = CH_3
R^4 = CH_3
For *Eudragit RL* and *Eudragit RS*:
R^1 = H, CH_3
R^2 = CH_3, C_2H_5
R^3 = CH_3
R^4 = $CH_2CH_2N(CH_3)_3^+Cl^-$
For *Eudragit NE 30 D* and *Eudragit NE 40 D*:
R^1, R^3 = H, CH_3
R^2, R^4 = CH_3, C_2H_5
For *Acryl-EZE* and *Acryl-EZE MP*; *Eudragit L 30 D-55* and *Eudragit L 100-55*, *Eastacryl 30D*, *Kollicoat MAE 30 D* and *Kollicoat MAE 30 DP*:
R^1, R^3 = H, CH_3
R^2 = H
R^4 = CH_3, C_2H_5

Table I: Chemical name and CAS Registry Number of polymethacrylates.

Chemical name	Trade name	Company name	CAS number
Poly(butyl methacrylate, (2-dimethylaminoethyl) methacrylate, methyl methacrylate) 1 : 2 : 1	*Eudragit E 100*	Röhm GmbH	[24938-16-7]
	Eudragit E 12.5	Röhm GmbH	
	Eudragit E PO	Röhm GmbH	
Poly(ethyl acrylate, methyl methacrylate) 2 : 1	*Eudragit NE 30 D*	Röhm GmbH	[9010-88-2]
	Eudragit NE 40 D	Röhm GmbH	
Poly(methacrylic acid, methyl methacrylate) 1 : 1	*Eudragit L 100*	Röhm GmbH	[25806-15-1]
	Eudragit L 12.5	Röhm GmbH	
	Eudragit L 12.5 P	Röhm GmbH	
Poly(methacrylic acid, ethyl acrylate) 1 : 1	*Acryl-EZE*	Colorcon	[25212-88-8]
	Acryl-EZE MP	Colorcon	
	Eudragit L 30 D-55	Röhm GmbH	
	Eudragit L 100-55	Röhm GmbH	
	Eastacryl 30D	Eastman Chemical	
	Kollicoat MAE 30 D	BASF Fine Chemicals	
	Kollicoat MAE 30 DP	BASF Fine Chemicals	
Poly(methacrylic acid, methyl methacrylate) 1 : 2	*Eudragit S 100*	Röhm GmbH	[25086-15-1]
	Eudragit S 12.5	Röhm GmbH	
	Eudragit S 12.5 P	Röhm GmbH	
Poly(methyl acrylate, methyl methacrylate, methacrylic acid) 7: 3:1	*Eudragit FS 30D*	Röhm GmbH	[26936-24-3]
Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.2	*Eudragit RL 100*	Röhm GmbH	[33434-24-1]
	Eudragit RL PO	Röhm GmbH	
	Eudragit RL 30 D	Röhm GmbH	
	Eudragit RL 12.5	Röhm GmbH	
	Eudragit RD 100	Röhm GmbH	
Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1	*Eudragit RS 100*	Röhm GmbH	[33434-24-1]
	Eudragit RS PO	Röhm GmbH	
	Eudragit RS 30 D	Röhm GmbH	
	Eudragit RS 12.5	Röhm GmbH	

6 Functional Category

Film former; tablet binder; tablet diluent.

7 Applications in Pharmaceutical Formulation or Technology

Polymethacrylates are primarily used in oral capsule and tablet formulations as film-coating agents.(1–17) Depending on the type of polymer used, films of different solubility characteristics can be produced; *see* Table II.

Eudragit E is used as a plain or insulating film former; it is soluble in gastric fluid below pH 5. In contrast, *Eudragit L*, *S* and *FS* types are used as enteric coating agents because they are resistant to gastric fluid. Different types are available that are soluble at different pH values: e.g. *Eudragit L* is soluble at pH > 6; *Eudragit S* and *FS* are soluble at pH > 7.

Eudragit RL, *RS*, *RD 100*, *NE 30 D* and *NE 40 D* are used to form water-insoluble film coats for sustained-release products. *Eudragit RL* films are more permeable than those of *Eudragit RS*, and films of varying permeability can be obtained by mixing the two types together.

Eudragit L 30 D-55 is used as an enteric coating film former for solid-dosage forms. The coating is resistant to gastric juice but dissolves readily at above pH 5.5.

Eudragit L 100-55 is an alternative to *Eudragit L 30 D-55*. It is commercially available as a redispersible powder.

Acryl-EZE and *Acryl-EZE MP* are also commercially available as redispersible powder forms, which are designed for enteric coating of tablets and beads, respectively.

Eastacryl 30 D, *Kollicoat MAE 30 D*, and *Kollicoat MAE 30 DP*, are aqueous dispersions of methacrylic acid–ethyl acrylate copolymers. They are also used as enteric coatings for solid-dosage forms.

Polymethacrylates are also used as binders in both aqueous and organic wet-granulation processes. Larger quantities (5–20%) of dry polymer are used to control the release of an active substance from a tablet matrix. Solid polymers may be used in direct-compression processes in quantities of 10–50%.

Polymethacrylate polymers may additionally be used to form the matrix layers of transdermal delivery systems and have also been used to prepare novel gel formulations for rectal administration.(18)

See also Section 18.

8 Description

Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. Several different types are commercially available and may be obtained as the dry powder, as an aqueous dispersion, or as an organic solution. A (60 : 40) mixture of acetone and propan-2-ol is most commonly used as the organic solvent. *See* Tables I and III.

Eudragit E is cationic polymer based on dimethylaminoethyl methacrylate and other neutral methacrylic acid esters. It

Table II: Summary of properties and uses of commercially available polymethacrylates.

Type	Supply form	Polymer dry weight content	Recommended solvents or diluents	Solubility/permeability	Applications
Eudragit (Röhm GmbH)					
Eudragit E 12.5	Organic solution	12.5%	Acetone, alcohols	Soluble in gastric fluid to pH 5	Film coating
Eudragit E 100	Granules	98%	Acetone, alcohols	Soluble in gastric fluid to pH 5	Film coating
Eudragit E PO	Powder	98%	Acetone, alcohols	Soluble in gastric fluid to pH 5	Film coating
Eudragit L 12.5 P	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
Eudragit L 12.5	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
Eudragit L 100	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
Eudragit L 100-55	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Eudragit L 30 D-55	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Eudragit S 12.5 P	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 7	Enteric coatings
Eudragit S 12.5	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 7	Enteric coatings
Eudragit S 100	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 7	Enteric coatings
Eudragit FS 30D	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 7	Enteric coatings
Eudragit RL 12.5	Organic solution	12.5%	Acetone, alcohols	High permeability	Sustained release
Eudragit RL 100	Granules	97%	Acetone, alcohols	High permeability	Sustained release
Eudragit RD 100	Powder	97%	Acetone, alcohols	High permeability	Rapid disintegrating Film
Eudragit RL PO	Powder	97%	Acetone, alcohols	High permeability	Sustained release
Eudragit RL 30 D	Aqueous dispersion	30%	Water	High permeability	Sustained release
Eudragit RS 12.5	Organic solution	12.5%	Acetone, alcohols	Low permeability	Sustained release
Eudragit RS 100	Granules	97%	Acetone, alcohols	Low permeability	Sustained release
Eudragit RS PO	Powder	97%	Acetone, alcohols	Low permeability	Sustained release
Eudragit RS 30 D	Aqueous dispersion	30%	Water	Low permeability	Sustained release
Eudragit NE 30 D	Aqueous dispersion	30%	Water	Swellable, permeable	Sustained release, tablet matrix
Eudragit NE 40 D	Aqueous dispersion	40%	Water	Swellable, permeable	Sustained release, tablet matrix
Eastacryl (Eastman Chemical)					
Eastacryl 30 D	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Kollicoat (BASF Fine Chemicals)					
Kollicoat 30 D	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Kollicoat 30 DP	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Acryl-EZE (Colorcon)					
Acryl-EZE	Powder	95%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Acryl-EZE MP	Aqueous dispersion	95%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings

Note: Recommended plasticizers for the above polymers include dibutyl phthalate, polyethylene glycols, triethyl citrate, triacetin, and 1,2-propylene glycol. The recommended concentration of the plasticizer is approximately 10–25% plasticizer (based on the dry polymer weight). A plasticizer is not necessary with *Eudragit E 12.5*, *Eudragit E 100* and *Eudragit NE 30 D*.

Table III: Solubility of commercially available polymethacrylates in various solvents.

Type	Solvent						
	Acetone and alcohols[a]	Dichloromethane	Ethyl acetate	1 N HCl	1 N NaOH	Petroleum ether	Water
Eudragit (Röhm GmbH)							
Eudragit E 12.5	M	M	M	M	—	M	—
Eudragit E 100	S	S	S	—	—	I	I
Eudragit L 12.5 P	M	M	M	—	M	P	P
Eudragit L 12.5	M	M	M	—	M	P	P
Eudragit L 100-55	S	I	I	—	S	I	I
Eudragit L 100	S	I	I	—	S	I	I
Eudragit L 30 D-55[b]	M[c]	—	—	M	—	M	—
Eudragit S 12.5 P	M	M	M	—	M	P	P
Eudragit S 12.5	M	M	M	—	M	P	P
Eudragit S 100	S	I	I	—	S	I	I
Eudragit RL 12.5	M	M	M	—	—	P	M
Eudragit RL 100	S	S	S	—	—	I	I
Eudragit RL PO	S	S	S	—	I	I	I
Eudragit RL 30 D[b]	M[c]	M	M	—	I	I	M
Eudragit RS 12.5	M	M	M	—	—	P	M
Eudragit RS 100	S	S	S	—	—	I	I
Eudragit RS PO	S	S	S	—	I	I	I
Eudragit RS 30 D[b]	M[c]	M	M	—	I	I	M
Eastacryl (Eastman Chemical Company)							
Eastacryl 30D[b]	M[c]	—	—	—	M	—	M
Kollicoat (BASF Fine Chemicals)							
Kollicoat MAE 30 D[b]	M[c]	—	—	—	M	—	M
Kollicoat MAE 30 DP[b]	M[c]	—	—	—	M	—	M
Acryl-EZE (Colorcon)							
Acryl-EZE	S	I	I	—	S	I	I
Acryl-EZE MP	S	I	I	—	S	I	I

S = soluble; M = miscible; I = insoluble or immiscible; P = precipitates.

[a] Alcohols including ethanol (95%), methanol, and propan-2-ol.

[b] Supplied as a milky-white aqueous dispersion.

[c] A 1 : 5 mixture forms a clear, viscous, solution.

1 part of *Eudragit RL 30 D* or of *Eudragit RS 30 D* dissolves completely in 5 parts acetone, ethanol (95%), or propan-2-ol to form a clear or slightly turbid solution. However, when mixed in a ratio of 1 : 5 with methanol, *Eudragit RL 30 D* dissolves completely, whereas *Eudragit RS 30 D* dissolves only partially.

is soluble in gastric fluid as well as in weakly acidic buffer solutions (up to pH ≈ 5). *Eudragit E* is available as a 12.5% ready-to-use solution in propan-2-ol–acetone (60 : 40). It is light yellow in color with the characteristic odor of the solvents. Solvent-free granules contain ≈98% dried weight content of *Eudragit E*. *Eudragit E PO* is a white free-flowing powder with at least 95% of dry polymer.

Eudragit L and *S*, also referred to as methacrylic acid copolymers in the USPNF 23 monograph, are anionic copolymerization products of methacrylic acid and methyl methacrylate. The ratio of free carboxyl groups to the ester is approximately 1 : 1 in *Eudragit L* (Type A) and approximately 1 : 2 in *Eudragit S* (Type B). Both polymers are readily soluble in neutral to weakly alkaline conditions (pH 6–7) and form salts with alkalis, thus affording film coats that are resistant to gastric media but soluble in intestinal fluid. They are available as a 12.5% solution in propan-2-ol without plasticizer (*Eudragit L 12.5* and *S 12.5*); and as a 12.5% ready-to-use solution in propan-2-ol with 1.25% dibutyl phthalate as plasticizer (*Eudragit L 12.5 P* and *S 12.5 P*). Solutions are colorless, with the characteristic odor of the solvent. *Eudragit L-100* and *Eudragit S-100* are white free-flowing powders with at least 95% of dry polymers.

Eudragit FS 30D is the aqueous dispersion of an anionic copolymer based on methyl acrylate, methyl methacrylate, and methacrylic acid. The ratio of free carboxyl groups to ester groups is approximately 1 : 10. It has been designed for the use in enteric-coated solid-dosage forms and dissolves in aqueous systems at pH >7.

Eudragit RL and *Eudragit RS*, also referred to as ammonio methacrylate copolymers in the USPNF 23 monograph, are copolymers synthesized from acrylic acid and methacrylic acid esters, with *Eudragit RL* (Type A) having 10% of functional quaternary ammonium groups and *Eudragit RS* (Type B) having 5% of functional quaternary ammonium groups. The ammonium groups are present as salts and give rise to pH-independent permeability of the polymers. Both polymers are water-insoluble, and films prepared from *Eudragit RL* are freely permeable to water, whereas, films prepared from *Eudragit RS* are only slightly permeable to water. They are available as 12.5% ready-to-use solutions in propan-2-ol–acetone (60 : 40). Solutions are colorless or slightly yellow in color, and may be clear or slightly turbid; they have an odor characteristic of the solvents. Solvent-free granules (*Eudragit RL 100* and *Eudragit RS 100*) contain ⩾97% of the dried weight content of the polymer.

Table IV: Specifications from PhEur 2005.

Test	PhEur 2005					
	Methacrylic acid–ethyl acrylate copolymer (1 : 1)[a]	**Methacrylic acid–ethyl acrylate copolymer (1 : 1) dispersion 30%[b]**	**Methacrylic acid–methyl methacrylate copolymer (1 : 1)[c]**	**Methacrylic acid–methyl methacrylate copolymer (1 : 2)[d]**	**Basic butylated methacrylate copolymer[e]**	**Polyacrylate dispersion 30%[f]**
Identification	+	+	+	+	+	+
Characters	+	+	+	+	+	+
Appearance of a film	+	+	+	+	+	+
Apparent viscosity	100–200 mPa s	$\leqslant$15 mPa s	50–200 mPa s	50–200 mPa s	3–6 mPa s	$\leqslant$50 mPa s
Particulate matter	—	$\leqslant$1.0%	—	—	—	$\leqslant$0.5%
Limit of monomers	—	—	—	—	$\leqslant$0.3%	$\leqslant$100 ppm
Ethyl acrylate and methacrylic acid	$\leqslant$0.1%	$\leqslant$0.1%	—	—	—	—
Methyl methacrylate and methacrylic acid	—	—	$\leqslant$0.1%	$\leqslant$0.1%	—	—
Residue on evaporation	—	0.285–0.315 g	—	—	—	0.285–0.315 g
Loss on drying	$\leqslant$5.0%	—	$\leqslant$5.0%	$\leqslant$5.0%	$\leqslant$2.0%	—
Heavy metals	—	—	—	—	$\leqslant$20 ppm	$\leqslant$20 ppm
Sulfated ash	$\leqslant$0.4%	$\leqslant$0.2%	$\leqslant$0.1%	$\leqslant$0.1%	$\leqslant$0.1%	$\leqslant$0.4%
Microbial contamination	—	$\leqslant 10^3$/g	—	—	—	$\leqslant 10^3$/g
Assay	Methacrylic acid units 46.0–50.6%	Methacrylic acid units 46.0–50.6%	Methacrylic acid units 46.0–50.6%	Methacrylic acid units 27.6–30.7%	Dimethylaminoethyl units 20.8–25.5%	Residue on evaporation 28.5%–31.5%

[a] Corresponds to *Eudragit L100-55.*

[b] Corresponds to *Eudragit L 30D-55.*

[c] Corresponds to *Eudragit L.*

[d] Corresponds to *Eudragit S.*

[e] Corresponds to *Eudragit E.*

[f] Corresponds to *Eudragit NE 30D.*

Eudragit RL PO and *Eudragit RS PO* are fine, white powders with a slight amine-like odor. They are characteristically the same polymers as *Eudragit RL* and *RS*. They contain $\geqslant$97% of dry polymer.

Eudragit RL 30 D and *Eudragit RS 30 D* are aqueous dispersions of copolymers of acrylic acid and methacrylic acid esters with a low content of quaternary ammonium groups. The dispersions contain 30% polymer. The quaternary groups occur as salts and are responsible for the permeability of films made from these polymers. Films prepared from *Eudragit RL 30 D* are readily permeable to water and to dissolved active substances, whereas films prepared from *Eudragit RS 30 D* are less permeable to water. Film coatings prepared from both polymers give pH-independent release of active substance. Plasticizers are usually added to improve film properties.

Eudragit RD100 is in the powder form, which can be redispersed in water and used as rapid disintegrating films. The composition for *Eudragit RD100* is *Eudragit RL100* and carboxymethylcellulose sodium (90 : 10).

Eudragit NE 30 D and *Eudragit NE 40 D* are aqueous dispersions of a neutral copolymer consisting of polymethacrylic acid esters. The dispersions are milky-white liquids of low viscosity and have a weak aromatic odor. Films prepared from the lacquer swell in water, to which they become permeable. Thus, films produced are insoluble in water, but give pH-independent drug release.

Eudragit L 30 D-55, is an aqueous dispersion of an anionic copolymer based on methacrylic acid and ethyl acrylate. The copolymer corresponds to USPNF 23 methacrylic acid copolymer, Type C. The ratio of free-carboxyl groups to ester groups is 1 : 1. Films prepared from the copolymers dissolve above pH 5.5, forming salts with alkalis, thus affording coatings that are insoluble in gastric media but soluble in the small intestine.

Eastacryl 30D, *Kollicoat MAE 30 D*, and *Kollicoat MAE 30 DP* are also aqueous dispersions of the anionic copolymer based on methacrylic acid and ethyl acrylate. The copolymer also corresponds to USPNF 23 methacrylic acid copolymer, Type C. The ratio of free-carboxyl groups to ester groups is 1 : 1. Films prepared from the copolymers dissolve above pH 5.5, forming salts with alkalis, thus affording coatings that are insoluble in gastric media, but soluble in the small intestine.

Eudragit L 100-55 (prepared by spray-drying *Eudragit L 30 D-55*) is a white, free-flowing powder that is redispersible in water to form a latex that has properties similar to those of *Eudragit L 30 D-55*.

Acryl-EZE and *Acryl-EZE MP* are also commercially available as redispersible powder forms, which are designed for enteric coating of tablets and beads, respectively.

9 Pharmacopeial Specifications

Specifications for polymethacrylates from the PhEur 2005 are shown in Table IV and those from the USPNF 23 in Table V.

10 Typical Properties

Acid value:
300–330 for *Eudragit L 12.5*, *L 12.5 P*, *L 100*, *L 30 D-55*, *L 100-55*, *Eastacryl 30D*, *Kollicoat MAE 30 D*, and *Kollicoat MAE 30 DP*.
180–200 for *Eudragit S 12.5*, *S 12.5 P*, and *S 100*.

Alkali value:
162–198 for *Eudragit E 12.5* and *E 100*;
23.9–32.3 for *Eudragit RL 12.5*, *RL 100*, and *RL PO*;
27.5–31.7 for *Eudragit RL 30 D*;
12.1–18.3 for *Eudragit RS 12.5*, *RS 100*, and *RS PO*;
16.5–22.3 for *Eudragit RS 30 D*.

Density (bulk): 0.390 g/cm^3

Density (tapped): 0.424 g/cm^3

Density (true):
0.811–0.821 g/cm^3 for *Eudragit E*;
0.83–0.85 g/cm^3 for *Eudragit L*, *S 12.5* and *12.5 P*;
1.058–1.068 g/cm^3 for *Eudragit FS 30D*;
0.831–0.852 g/cm^3 for *Eudragit L*, *S 100*;
1.062–1.072 g/cm^3 for *Eudragit L 30 D-55*;
0.821–0.841 g/cm^3 for *Eudragit L 100-55*;
0.816–0.836 g/cm^3 for *Eudragit RL* and *RS 12.5*;
0.816–0.836 g/cm^3 for *Eudragit RL* and *RS PO*;
1.047–1.057 g/cm^3 for *Eudragit RL* and *RS 30 D*;
1.037–1.047 g/cm^3 for *Eudragit NE 30D*;
1.062–1.072 g/cm^3 for *Eastacryl 30D*;
1.062–1.072 g/cm^3 for *Kollicoat MAE 30 D* and *Kollicoat MAE 30 DP*.

Refractive index:
n_D^{20} = 1.38–1.385 for *Eudragit E*;
n_D^{20} = 1.39–1.395 for *Eudragit L* and *S*;
n_D^{20} = 1.387–1.392 for *Eudragit L 100-55*;
n_D^{20} = 1.38–1.385 for *Eudragit RL* and *RS*.

Solubility: *see* Table II.

Viscosity (dynamic):
3–12 mPa s for *Eudragit E*;
$\leqslant$50 mPa s for *Eudragit NE 30D*;
50–200 mPa s for *Eudragit L* and *S*;
$\leqslant$20 mPa s for *Eudragit FS 30D*;
$\leqslant$15 mPa s for *Eudragit L 30 D-55*;
100–200 mPa s for *Eudragit L 100-55*;
$\leqslant$15 mPa s for *Eudragit RL* and *RS*;
$\leqslant$200 mPa s for *Eudragit RL* and *RS 30D*;
$\leqslant$15 mPa s for *Kollicoat MAE 30 D* and *Kollicoat MAE 30 DP*;
145 mPa s for *Eastacryl 30D*.

11 Stability and Storage Conditions

Dry powder polymer forms are stable at temperatures less than 30°C. Above this temperature, powders tend to form clumps, although this does not affect the quality of the substance and the clumps can readily be broken up. Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 30°C.

Dispersions are sensitive to extreme temperatures and phase separation occurs below 0°C. Dispersions should therefore be stored at temperatures between 5 and 25°C and are stable for at least 18 months after shipping from the manufacturer's warehouse if stored in a tightly closed container at the above conditions.

12 Incompatibilities

Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent. For example, coagulation may be caused by soluble electrolytes, pH changes, some organic solvents, and extremes of temperature; *see* Table II. For example, dispersions of *Eudragit L 30 D*, *RL 30 D*, *L 100-55*, and *RS 30 D* are incompatible with magnesium stearate. *Eastacryl 30D*, *Kollicoat MAE 30 D*, and *Kollicoat MAE 30 DP* are also incompatible with magnesium stearate.

Interactions between polymethacrylates and some drugs can occur, although solid polymethacrylates and organic solutions are generally more compatible than aqueous dispersions.

13 Method of Manufacture

Prepared by the polymerization of acrylic and methacrylic acids or their esters, e.g. butyl ester or dimethylaminoethyl ester.

14 Safety

Polymethacrylate copolymers are widely used as film-coating materials in oral pharmaceutical formulations. They are also used in topical formulations and are generally regarded as nontoxic and nonirritant materials.

A daily intake of 2 mg/kg body-weight of *Eudragit* (equivalent to approximately 150 mg for an average adult) may be regarded as essentially safe in humans.

See also Section 15.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Additional measures should be taken when handling organic solutions of polymethacrylates. Eye protection, gloves, and a dust mask or respirator are recommended. Polymethacrylates should be handled in well-ventilated environment and measures should be taken to prevent dust formation.

Acute and chronic adverse effects have been observed in workers handling the related substances methyl methacrylate and poly(methyl methacrylate) (PMMA).(19,20) In the UK, the occupational exposure limit for methyl methacrylate has been set at 208 mg/m^3 (50 ppm) long-term (8-hour TWA), and 416 mg/m^3 (100 ppm) short-term.(21)

See also Section 17.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Methyl methacrylate; poly(methyl methacrylate).

Methyl methacrylate

Empirical formula: $C_5H_8O_2$

Molecular weight: 100.13

CAS number: [80-62-6]

Synonyms: methacrylic acid, methyl ester; methyl 2-methacrylate; methyl 2-methylpropenoate; MME.

Safety:
LD_{50} (dog, SC): 4.5 g/kg
LD_{50} (mouse, IP): 1 g/kg
LD_{50} (mouse, oral): 5.2 g/kg

Table V: Specifications from USPNF 23

Test	**USPNF 23**		
	Ammonio methacrylate copolymer[a]	**Methacrylic acid copolymer**[b]	**Methacrylic acid copolymer dispersion**[c]
Identification	+	+	+
Viscosity			
Type A	≤15 mPa s	50–200 mPa s	—
Type B	≤15 mPa s	50–200 mPa s	—
Type C	—	100–200 mPa s	≤15 mPa s
Loss on drying			
Type A	≤3.0%	≤5.0%	—
Type B	≤3.0%	≤5.0%	—
Type C	—	≤5.0%	68.5–71.5%[d]
Residue on ignition			
Type A	≤0.1%	≤0.1%	—
Type B	≤0.1%	≤0.1%	—
Type C	—	≤0.4%	≤0.2%[d]
Heavy metals	≤0.002%	≤0.002%	≤0.002%[d]
Organic volatile impurities	—	+	—
Limit of monomers	—	≤0.05%	≤0.01%
Limit of methyl methacrylate	≤0.005%	—	—
Limit of ethyl acrylate	≤0.025%	—	—
Coagulum content	—	—	≤1%[d]
Assay (dried basis)	Ammonio methacrylate units	Methacrylic acid units	Methacrylic acid units
Type A	8.85–11.96%	46.0–50.6%	—
Type B	4.48–6.77%	27.6–30.7%	—
Type C	—	46.0–50.6%	46.0–50.6%

[a] Corresponds to *Eudragit RL* and *RS*.

[b] Corresponds to *Eudragit L, S* and *L100-55*.

[c] Corresponds to *Eudragit L 30D-55*.

[d] Calculated based on undried dispersion basis.

LD_{50} (mouse, SC): 6.3 g/kg
LD_{50} (rat, IP): 1.33 g/kg
LD_{50} (rat, SC): 7.5 g/kg

Comments: methyl methacrylate forms the basis of acrylic bone cements used in orthopedic surgery.

Poly(methyl methacrylate)

Empirical formula: $(C_5H_8O_2)_n$

Synonyms: methyl methacrylate polymer; PMMA.

Comments: poly(methyl methacrylate) has been used as a material for intraocular lenses, for denture bases, and as a cement for dental prostheses.

18 Comments

A number of different polymethacrylates are commercially available that have different applications and properties; *see* Table II.

For spray coating, polymer solutions and dispersions should be diluted with suitable solvents. Some products need the addition of a plasticizer such as dibutyl sebacate, dibutyl phthalate, glyceryl triacetate, or polyethylene glycol. Different types of plasticizer may be mixed to optimize the polymer properties for special requirements.

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21 Authors

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22 Date of Revision

20 May 2005.

Poly(methyl vinyl ether/maleic anhydride)

1 Nonproprietary Names

None adopted.

2 Synonyms

Butyl ester of poly(methylvinyl ether–co-maleic anhydride); calcium and sodium salts of poly(methylvinyl ether–co-maleic anhydride); *Gantrez AN-119*; *Gantrez AN-139*; *Gantrez AN-149*; *Gantrez AN-169*; *Gantrez AN-179*; *Gantrez AN-903*; *Gantrez ES-225*; *Gantrez ES-425*; *Gantrez S-95*; *Gantrez S-96*; *Gantrez S-97*; *Gantrez MS-955*.

3 Chemical Name and CAS Registry Number

See Table I.

4 Empirical Formula and Molecular Weight

$(C_4H_2O_3\cdot C_3H_6O)_x$ *See* Table II.

5 Structural Formula

See Section 4.

6 Functional Category

Bioadhesive; color dispersant; complexing agent; emulsion stabilizer; film former; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Poly(methylvinyl ether/maleic anhydride) copolymers and derivatives are used in denture adhesive bases,(1) controlled-release coatings, enteric coatings, ostomy adhesives,(2) transdermal patches,(3) toothpastes,(4) mouthwashes,(5) and transdermal gels.(6,7) *Gantrez AN-119* has been used to manufacture specific bioadhesive ligand-nanoparticle conjugates(8) to aid gastrointestinal retention for oral drug delivery applications. More recently *Gantrez* has been utilized to develop novel polyethylene surface-modified medical devices with enhanced hydrophilicity and wettability.(9)

Table II: Molecular weights of selected commercially available copolymers of poly(methylvinyl ether/maleic anhydride)

Grade	Approximate molecular weight
Gantrez AN-119	200 000
Gantrez AN-903	800 000
Gantrez AN-139	1 000 000
Gantrez AN-169	2 000 000
Gantrez S-96	700 000
Gantrez S-97 (powder)	1 200 000
Gantrez S-97 (solution)	1 500 000
Gantrez MS-995	1 000 000
Gantrez ES-225	100 000–150 000
Gantrez ES-425	90 000–150 000

8 Description

In the solid state, poly(methylvinyl ether/maleic anhydride) copolymers are a white to off-white free flowing, odorless, hygroscopic powders. In solution, poly(methylvinyl ether/maleic anhydride) is a slightly hazy, odorless, viscous liquid.

9 Pharmacopeial Specifications

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10 Typical Properties

See Table III.

Table I: Chemical name and CAS registry number for poly(methylvinyl ether/maleic anhydride) copolymers and derivatives.

Chemical name	Trade name	CAS number
Poly(methylvinyl ether/maleic anhydride)	*Gantrez AN-119* *Gantrez AN-903* *Gantrez AN-139* *Gantrez AN-149* *Gantrez AN-169* *Gantrez AN-179*	[9011-16-9]
Poly(methylvinyl ether/maleic acid)	*Gantrez S-95* *Gantrez S-96* *Gantrez S-97*	[25153-40-6]
Monoethyl ester of poly(methylvinyl ether/maleic acid) (48–52%) in ethanol (48–52%)	*Gantrez ES-225 50% Alcoholic Solution*	[25087-06-3] [64-17-5]
Mixture of monoethyl ester of poly(methylvinyl ether/maleic acid) and monobutyl ester of poly(methylvinyl ether/maleic acid) (48–52%) in ethanol (43–47%) and *n*-butyl alcohol (≈5%)	*Gantrez ES-425 50% Alcoholic Solution*	[25087-06-3] [25119-68-0] [64-17-5] [200-751-6]
Mixed sodium/calcium salts of poly(methylvinyl ether/maleic anhydride)	*Gantrez MS-955*	[62386-95-2]

Table III: Typical physical properties of selected commercially available copolymers of poly(methylvinyl ether/maleic anhydride)

Grade	Specific viscosity (1% in MEK)	*Tg* (°C)	Specific gravity (25°C, 5% solids)	Bulk density (g/cm^3)	Polydispersity (Mn/Mw)	Moisture content (% w/w)	Viscosity (mPa s) of 5% w/w solution at 25°C	Dissociation constant
Gantrez AN **copolymers**								
AN-119	0.1–0.5	152	1.018	0.34	2.74	<1	15	—
AN-903	0.8–1.2	156	1.017	0.33	—	—	30	—
AN-139	1.0–1.5	151	1.016	0.33	3.47	<1	40	—
AN-149	1.5–2.5	153	1.017	0.35	2.58	<1	45	—
AN-169	2.5–3.5	154	1.017	0.32	2.06	<1	85	—
AN-179	3.5–5.0	154	1.017	0.33	2.12	<1	135	—
Gantrez S **copolymers**								
S-95	1.0–2.0	139	1.015	—	2.71	$\leqslant 17$	20	3.51–6.41
S-96 Solution	≈ 4.0	—	—	—	—	86–88	150	3.51–6.41
S-97	4.0–10.0	143	1.015	—	2.06	$\leqslant 6$	70	3.47–6.47
S-97 Solution	4.0–10.0	—	—	—	—	86–88	1000	3.50–6.50
Gantrez ES **and** ***MS*** **copolymers**								
ES-225	0.36–0.45	102	0.983	—	2.5–3.0	$\leqslant 0.5$	18,800	5.33
ES-425	0.37–0.45	96	0.977	—	2.5–3.4	$\leqslant 0.5$	14,400	5.28
MS-955	—	—	1.061[a]	—	2.3	$\leqslant 15$	700–3000[b]	—

[a] 13% solids at 30°C.

[b] Viscosity of 11.1% solids aqueous solution.

11 Stability and Storage Conditions

Poly(methylvinyl ether/maleic anhydride) and related free acids are hygroscopic powders and therefore excessive exposure to moisture should be avoided. Aqueous solutions exhibit decreases in viscosity upon exposure to UV light. Poly(methylvinyl ether/maleic anhydride) should be stored in a cool, dry place out of direct sunlight.

12 Incompatibilities

Poly(methylvinyl ether/maleic anhydride) and copolymers are incompatible with strong oxidizing agents and reducing agents, concentrated nitric acid, sulfuric acid, nitrofoam, oleum, potassium *t*-butoxide, aluminum, aluminum triisopropoxide, and crotonaldehyde. In addition, the anhydride will hydrolyze in water to form a water-soluble free acid that can subsequently be ionized to form salts in the presence of cations (Na^+, Zn^{2+}, Ca^{2+}, and Al^{3+}). Excessive addition of bivalent and trivalent metal ions to aqueous solution will result in precipitation, particularly in solutions containing high polymer concentrations.

13 Method of Manufacture

Poly(methylvinyl ether/maleic anhydride) and copolymers are manufactured from methylvinyl ether and maleic anhydride. The *S*, *ES*, and *MS* grades of *Gantrez* are manufactured by dispersing *AN* copolymers in a number of different solvents or salt solutions.(10)

14 Safety

Poly(methylvinyl ether/maleic anhydride) and copolymers are widely used in a diverse range of topical and oral pharmaceutical formulations.(11) These copolymers are generally regarded as nontoxic and nonirritant. Moreover, the dry powders and aqueous solutions are nonirritating with the exception of *ES*, *MS*, and *A* grades, which are irritating to the eye and may cause tissue damage.

LD_{50} (rat, oral): 8 g/kg (*Gantrez AN-130 Powder*)(10)
LD_{50} (rat, oral): 40 ml/kg (*Gantrez AN-139* 20% w/w aqueous solution)
LD_{50} (rat, oral): <25.6 g/kg (*Gantrez ES-225*)
LD_{50} (rat, oral): 25.6 g/kg (*Gantrez ES-425* 40% w/v corn oil solution)
LD_{50} (rat, oral): 25.6 g/kg (*Gantrez MS-955* 20% aqueous solution)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Excessive dust generation should be avoided when using powders, and an appropriate ventilation area and dust mask are recommended. Hand and eye protection is also recommended. The *A*, *ES*, and *MS* copolymers are extremely irritating to the eyes and a NIOSH-approved respirator and suitable eye protection are recommended when using *Gantrez ES-435*, *Gantrez ES-225*, and *Gantrez A-425*.

16 Regulatory Status

GRAS listed. Included in nonparenteral medicines licensed in the UK.

17 Related Substances

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18 Comments

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22 Date of Revision

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Polyoxyethylene Alkyl Ethers

1 Nonproprietary Names

The polyoxyethylene alkyl ethers are a series of polyoxyethylene glycol ethers of *n*-alcohols (lauryl, oleyl, myristyl, cetyl, and stearyl alcohol). Of the large number of different materials commercially available, four types are listed in the USPNF 23, one type in the JP 2001, and four types in the PhEur 2005.

BP: Macrogol cetostearyl ether
Macrogol lauryl ether
Macrogol oleyl ether
Macrogol stearyl ether
JP: Lauromacrogol
PhEur: Macrogoli aether cetostearylicus
Macrogoli aether laurilicum
Macrogoli aether oleicum
Macrogoli aether stearylicus
USPNF: Polyoxyl 20 cetostearyl ether
Polyoxyl 10 oleyl ether
Polyoxyl lauryl ether
Polyoxyl stearyl ether

Polyoxyethylene alkyl ethers are employed extensively in cosmetics, where the CTFA names laureth-*N*, myreth-*N*, ceteth-*N*, and steareth-*N* are commonly used. In this nomenclature, *N* is the number of ethylene oxide groups, e.g. steareth-20.

See also Sections 2–5.

2 Synonyms

Polyoxyethylene alkyl ethers are nonionic surfactants produced by the polyethoxylation of linear fatty alcohols. Products tend to be mixtures of polymers of slightly varying molecular weights and the numbers used to describe polymer lengths are average values.

Two systems of nomenclature are used to describe these materials. The number '10' in the name *Texofor A10* refers to the approximate polymer length in oxyethylene units (i.e. *y*, *see* Section 5). The number '1000' in the name 'cetomacrogol 1000' refers to the average molecular weight of the polymer chain.

Synonyms applicable to polyoxyethylene alkyl ethers are shown below.

Brij; *Cremophor A*; *Cyclogol 1000*; *Empilan KB*; *Empilan KM*; *Emulgen*; *Ethylan* C; macrogol ethers; *Marlowet*; *Plurafac*; *Procol*; *Ritoleth*; *Ritox*; *Texofor A*; *Volpo*.

Table I shows synonyms for specific materials.

3 Chemical Name and CAS Registry Number

Polyethylene glycol monocetyl ether [9004-95-9]
Polyethylene glycol monolauryl ether [9002-92-0]
Polyethylene glycol monooleyl ether [9004-98-2]
Polyethylene glycol monostearyl ether [9005-00-9]

4 Empirical Formula and Molecular Weight

See Sections 1, 2, and 5.

5 Structural Formula

$CH_3(CH_2)_x(OCH_2CH_2)_yOH$

In the formula, $(x + 1)$ is the number of carbon atoms in the alkyl chain, typically:

12 lauryl (dodecyl)
14 myristyl (tetradecyl)
16 cetyl (hexadecyl)
18 stearyl (octadecyl)

and *y* is the number of ethylene oxide groups in the hydrophilic chain, typically 10–60.

The polyoxyethylene alkyl ethers tend to be mixtures of polymers of slightly varying molecular weights, and the

Table I: Synonyms of selected polyoxyethylene alkyl ethers.

Name	Synonym
Cetomacrogol 1000	Polyethylene glycol 1000; macrocetyl ether; polyoxyethylene glycol 1000 monocetyl ether; *Cresmer 1000*.
Polyoxyl 6 cetostearyl ether	*Ceteareth 6*; *Cremophor A6*; *Volpo CS6*.
Polyoxyl 20 cetostearyl ether	*Atlas G-3713*; *Ceteareth 20*; *Cremophor A 20 polyether*; *Volpo CS20*.
Polyoxyl 25 cetostearyl ether	*Ceteareth 25*; *Cremophor A25*; *Volpo CS25*.
Polyoxyl 2 cetyl ether	*Brij 52*; ceteth-2; *Lipocol C-2*; *Procol CA-2*.
Polyoxyl 10 cetyl ether	*Brij 56*; ceteth-10; *Lipocol C-10*; *Procol CA-10*.
Polyoxyl 20 cetyl ether	*Brij 58*; ceteth-20; *Lipocol C-20*; *Volpo C20*.
Polyoxyl 4 lauryl ether	*Brij 30*; laureth-4; *Lipocol L-4*; *Procol LA-4*; *Tego Alkanol L4*; *Volpo L4*.
Polyoxyl 9 lauryl ether	Laureth-9; lauromacrogol 400; polidocanol; *Volpo L9*.
Polyoxyl 23 lauryl ether	*Brij 35*; laureth-23; *Lipocol L-23*; *Procol LA-23*; *Ritox 35*; *Tego Alkanol L23 P*.
Polyoxyl 2 oleyl ether	*Brij 92*; *Brij 93*; oleth-2; *Lipocol O-2*; *Procol 0A-2*; *Ritoleth 2*;*Volpo N2*.
Polyoxyl 10 oleyl ether	*Brij 96*; *Brij 97*; oleth-10; polyethylene glycol monooleyl ether; *Lipocol O-10*; *Procol OA-10*; *Ritoleth 10*; *Volpo N 10*.
Polyoxyl 20 oleyl ether	*Brij 98*; *Brij 99*; *Lipocol O-20*; oleth-20; *Procol OA-20*; *Ritoleth 20*; *Volpo N 20*.
Polyoxyl 2 stearyl ether	*Brij 72*; *Lipocol S-2*; *Procol SA-2;* steareth-2; *Tego Alkanol S2*; *Volpo S-2*.
Polyoxyl 10 stearyl ether	*Brij 76*; *Lipocol S-10*; *Procol SA-10*; steareth-10; *Tego Alkanol S10*; *Volpo S-10*.
Polyoxyl 21 stearyl ether	*Brij 721*; *Ritox 721*; *steareth-21*.
Polyoxyl 100 stearyl ether	*Brij 700*; steareth-100.

numbers quoted are average values. In cetomacrogol 1000, for example, *x* is 15 or 17, and *y* is 20–24.

6 Functional Category

Emulsifying agent; penetration enhancer; solubilizing agent; wetting agent.

7 Applications in Pharmaceutical Formulation or Technology

Polyoxyethylene alkyl ethers are nonionic surfactants widely used in topical pharmaceutical formulations and cosmetics, primarily as emulsifying agents for water-in-oil and oil-in-water emulsions; and the stabilization of microemulsions and multiple emulsions.

Polyoxyethylene alkyl ethers are used as solubilizing agents for essential oils, perfumery chemicals, vitamin oils, and drugs of low-water solubility such as cortisone acetate, griseofulvin, menadione,(1) chlordiazepoxide(2) and cholesterol.(3) They have applications as antidusting agents for powders; wetting and dispersing agents for coarse-particle liquid dispersions; and detergents, especially in shampoos, face washes and similar cosmetic cleaning preparations. They are used as gelling and foaming agents (e.g. *Brij 72* gives a quick-breaking foam, while *Brij 97* (15–20%), *Volpo N* series and *Cremophor A25* (21–30%) give clear gels).

Polyoxyethylene alkyl ethers have been used in formulation of oleosomes, hydrosomes, phosphosomes, vesicles(4) and niosomes.(5,6) An increased flux of estradiol niosomes through human stratum corneum *in vitro* has been demonstrated.(7)

Polyoxyethylene alkyl ethers have been found to have an enhancing effect on the skin permeation of drugs such as ibuprofen,(8) methyl nicotinate,(9) and clotrimazole.(10) Enhanced ocular absorption of insulin from eye drops,(11) and an ocular insert device,(12) have been observed using polyoxyethylene alkyl ethers in the formulation systems. Increased buccal absorption of verapamil through porcine esophageal mucosa has also been reported.(13)

Polyoxyethylene alkyl ethers have also been used in suppository formulations to increase the drug release from the suppository bases.(14–16)

Polyoxyethylene alkyl ethers (especially laureth-23) have been used as a solubilizer and coating agent to provide hydrophilicity to polymeric nanoparticles.(17–19)

Polyoxyethylene alkyl ethers such as polidocanol are suitable for use in injectable formulations as a solubilizer or dispersant.(20)

8 Description

Polyoxyethylene alkyl ethers vary considerably in their physical appearance from liquids, to pastes, to solid waxy substances. They are colorless, white, cream-colored or pale yellow materials with a slight odor.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for polyoxyethylene alkyl ethers.

Test	JP 2001	PhEur 2005	PhEur 2005	PhEur 2005	PhEur 2005	USPNF 23	USPNF 23	USPNF 23	USPNF 23
	Lauromacrogol	Macrogol cetostearyl ether	Macrogol stearyl ether	Macrogol lauryl ether	Macrogol oleyl ether	Polyoxyl 20 cetostearyl ether	Polyoxyl 10 oleyl ether	Polyoxyl lauryl ether	Polyoxyl stearyl ether
Appearance of solution	—	+	+	+	+	—	—	+	+
Identification	+	+	+	+	+	+	+	+	+
Characters	+	+	+	+	+	—	—	—	—
Water	—	⩽3.0%	⩽3.0%	⩽3.0%	⩽3.0%	⩽1.0%	⩽3.0%	⩽3.0%	⩽3.0%
pH (10% solution)	—	—	—	—	—	4.5–7.5	—	—	—
Alkalinity	—	+	+	+	+	—	—	+	+
Acidity	+	—	—	—	—	—	—	—	—
Residue on ignition	⩽0.20%	—	—	—	—	⩽0.4%	⩽0.4%	—	—
Heavy metals	—	—	—	—	—	⩽0.002%	⩽0.002%	—	—
Acid value	—	⩽1.0	⩽1.0	⩽1.0	⩽1.0	⩽0.5	⩽1.0	⩽1.0	⩽1.0
Hydroxyl value	—	+	+	+	+	42–60	75–95	+	+
Iodine value	—	⩽2.0	⩽2.0	⩽2.0	+	—	23–40	⩽2.0	⩽2.0
Saponification value	—	⩽3.0	⩽3.0	⩽3.0	⩽3.0	⩽2.0	⩽3.0	⩽3.0	⩽3.0
Free polyethylene glycols	—	—	—	—	—	⩽7.5%	⩽7.5%	—	—
Free ethylene oxide	—	⩽1 ppm	⩽1 ppm	⩽1 ppm	⩽1 ppm	⩽0.01%	⩽0.01%	⩽1 μg/g	⩽1 μg/g
Dioxan	—	⩽10 ppm	⩽10 ppm	⩽10 ppm	⩽10 ppm	—	—	⩽10 μg/g	⩽10 μg/g
Peroxide value	—	—	—	—	⩽10.0	—	—	—	—
Average polymer length	—	—	—	—	—	17.2–25.0	8.6–10.4	≈3.0–23.0	≈2.0–20.0
Organic volatile impurities	—	—	—	—	—	+	+	—	—
Total ash	—	⩽0.2%	—	⩽0.2%	⩽0.2%	—	—	⩽0.2%	—

10 Typical Properties

See Tables III and IV.

11 Stability and Storage Conditions

Polyoxyethylene alkyl ethers are chemically stable in strongly acidic or alkaline conditions. The presence of strong electrolytes may, however, adversely affect the physical stability of emulsions containing polyoxyethylene alkyl ethers.

On storage, polyoxyethylene alkyl ethers can undergo autoxidation, resulting in the formation of peroxides with an increase in acidity. Many commercially available grades are thus supplied with added antioxidants. Typically, a mixture of 0.01% butylated hydroxyanisole and 0.005% citric acid is used for this purpose.

Polyoxyethylene alkyl ethers should be stored in an airtight container, in a cool, dry place.

12 Incompatibilities

Discoloration or precipitation may occur with iodides, mercury salts, phenolic substances, salicylates, sulfonamides, and tannins. Polyoxyethylene alkyl ethers are also incompatible with benzocaine, tretinoin(21) and oxidizable drugs.(22)

The antimicrobial efficacy of some phenolic preservatives, such as the parabens, is reduced owing to hydrogen bonding. Cloud points are similarly depressed by phenols owing to hydrogen bonding between ether oxygen atoms and phenolic hydroxyl groups. Salts, other than nitrates, iodides, and thiocyanates (which cause an increase) can also depress cloud points.(23)

13 Method of Manufacture

Polyoxyethylene alkyl ethers are prepared by the condensation of linear fatty alcohols with ethylene oxide. The reaction is controlled so that the required ether is formed with the polyethylene glycol of the desired molecular weight.

14 Safety

Polyoxyethylene alkyl ethers are used as nonionic surfactants in a variety of topical pharmaceutical formulations and cosmetics. The polyoxyethylene alkyl ethers form a series of materials with varying physical properties and manufacturers' literature should be consulted for information on the applications and safety of specific materials.

Although generally regarded as essentially nontoxic and nonirritant materials, some polyoxyethylene alkyl ethers, particularly when used in high concentration (>20%), appear to have a greater irritant potential than others.

Animal toxicity studies suggest that polyoxyethylene alkyl ethers have a similar oral toxicity to other surfactants and can be regarded as being moderately toxic.

Polyoxyethylene cetyl ether:(24)

LD_{50} (mouse, oral): 2.60 g/kg
LD_{50} (rabbit, skin): 40 g/kg/4 week intermittent
LD_{50} (rat, oral): 2.50 g/kg

Polyoxyethylene lauryl ether:(24)

LD_{50} (mouse, IP): 0.16 g/kg
LD_{50} (mouse, IV): 0.10 g/kg
LD_{50} (mouse, oral): 4.94 g/kg
LD_{50} (mouse, SC): 0.79 g/kg
LD_{50} (rat, IV): 0.027 g/kg
LD_{50} (rat, oral): 8.60 g/kg
LD_{50} (rat, SC): 0.95 g/kg

Polyoxyethylene oleyl ether:(24)

LD_{50} (rat, oral): 25.8 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16 Regulatory Status

Included in nonparenteral medicines licensed in the USA and UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Nonionic emulsifying wax.

18 Comments

Many other polyoxyethylene ethers are commercially available and are also used as surfactants. In addition to their surfactant properties, the series of polyoxyethylene ethers with lauryl side chains, e.g. nonoxynol 10, are also widely used as spermicides.

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Table III: Typical properties of selected commercially available grades of polyoxyethylene alkyl ethers.

Name	Physical form	Acid value	HLB value	Hydroxyl value	Iodine number	Saponification value	Density (g/cm^3) at 20°C unless otherwise stated	Water content (%)	Boiling point (°C)	Melting point or pour point (°C)	Cloud point (°C) for 1% aqueous solution	pH aqueous solution
Brij 30	Colorless to pale yellow liquid	⩽2	9.7	145–165	—	—	≈0.95 at 25°C	⩽1.0	>100	≈2	—	—
Brij 35	White waxy solid	⩽5	16.9	40–60	—	—	≈1.05 at 25°C	⩽3.0	>100	≈33	—	—
Brij 52	White waxy solid	⩽1	5.3	160–180	—	—	≈0.95	⩽1.0	—	33	—	5–8 (10% in 1 : 1 IPA: water)
Brij 56	White waxy solid	⩽1	12.9	75–90	—	—	≈1.06 at 25°C	⩽3.0	—	31	—	—
Brij 58	White solid	⩽1	15.7	45–60	—	—	1.02 at 25°C	⩽3.0	—	38	—	—
Brij 72	White waxy solid	⩽1	4.9	150–170	—	—	≈0.97 at 25°C	⩽1.0	—	43	—	—
Brij 76	White waxy solid	⩽1	12.4	75–90	—	—	≈1.05 at 25°C	⩽3.0	>100	38	—	5–8 (10% in 1 : 1 IPA : water)
Brij 78	White solid pellets	⩽1	15.3	45–60	—	—	≈1.09 at 25°C	⩽3.0	—	38	—	5–8 (10% in 1 : 4 IPA : water)
Brij 721	White to ivory solid pellets or flakes	<2	15.5	44–61	—	—	≈1.0 at 25°C	⩽2.0	—	45	—	—
Brij 93Veg	Pale yellow liquid	⩽1	4.9	160–180	—	—	≈0.9 at 25°C	⩽1.0	>100	10	—	5–8 (10% in 1 : 1 IPA : water)
Brij 97	White to pale yellow liquid to semi-solid	⩽1	12.4	80–95	—	—	≈1.0 at 25°C	⩽3.0	>100	16	>100	>100
Brij 98	Cream soft waxy solid	⩽1	15.3	50–65	—	—	≈1.07 at 25°C	⩽3.0	>100	33	—	5–8 (10% in 1 : 4 IPA : water)
Cremophor A6	White waxy substance	⩽1	10–12	115–134	⩽1	⩽3	0.896–0.906 at 60°C	⩽1.0	—	41–45	—	—
Cremophor A 20 polyether	White flakes	—	—	—	—	—	0.98% at 70°C	—	>149	56	—	—
Cremophor A25	White to off-white micro beads	⩽1	15–17	36–45	⩽1	⩽3	1.020–1.028 at 60°C	⩽1.0	—	44–48	—	5–7 (10%)
Emulgen 104P	Clear liquid	—	9.6	—	—	—	—	—	—	—	—	—
Emulgen 123P	White solid	—	16.9	—	—	—	—	—	—	—	>100	—
Emulgen 210P	Light yellow solid	—	10.7	—	—	—	—	—	—	—	—	—
Emulgen 220	Light yellow solid	—	14.2	—	—	—	—	—	—	—	98	—
Emulgen 320P	White solid	—	13.9	—	—	—	—	—	—	—	91	—
Emulgen 409P	Light yellow liquid	—	12.0	—	—	—	—	—	—	—	55	—
Ethosperse 1A4	—	⩽2	—	145–160	—	—	0.95	⩽0.5	—	—	—	—
Ethosperse 1A12	—	⩽2	—	72–82	—	—	1.10	⩽1.0	—	—	—	—
Ethosperse TDA6	—	⩽1	—	118–133	—	—	0.98	⩽1.0	—	—	—	—
Ethosperse S120	—	⩽0.5	—	385–430	—	—	1.16	⩽1.0	—	—	—	—
Ethosperse G26	—	⩽2	—	133–142	—	—	1.12 at 38°C	⩽0.5	—	—	—	—
Ethylan D252	Liquid	—	5.6	—	—	—	0.903	⩽0.5	—	5	Insoluble	—
Ethylan 253	Liquid	—	7.8	—	—	—	0.930	⩽0.5	—	3	Insoluble	—
Ethylan 254	Liquid	—	9.8	—	—	—	0.948	⩽3.0	—	5	Insoluble	—
Ethylan 256	Liquid	—	11.4	—	—	—	0.972	⩽0.5	—	15	43	—
Ethylan 257	Liquid	—	12.2	—	—	—	0.974 at 40°C	⩽0.5	—	21	49	—
Ethylan 2512	Solid	—	14.2	—	—	—	1.001	⩽0.5	—	29	92	—

Name	Physical form	Acid value	HLB value	Hydroxyl value	Iodine number	Saponification value	Density (g/cm^3) at 20°C unless otherwise stated	Water content (%)	Boiling point (°C)	Melting point or pour point (°C)	Cloud point (°C) for 1% aqueous solution	pH aqueous solution
Ethylan 2560	Solid	—	18.6	—	—	—	—	⩽0.5	—	45	>100	—
Plurafac RA20	Colorless hazy liquid	—	10.0	69–78	—	0.9965	0.988 at 25°C	⩽0.2	—	—	45	5.0–6.5 (1%)
Plurafac RA30	Colorless liquid	—	9.0	85–95	—	—	0.971 at 25°C	⩽0.2	—	10	36	5.0–6.5 (1%)
Plurafac RA40	Clear liquid	—	7.0	65–75	—	—	0.974 at 25°C	⩽0.2	—	–26	25	5.0–6.5 (1%)
Plurafac RA43	White opaque liquid	—	7.0	—	—	—	0.974 at 25°C	⩽0.4	—	–6	—	—
Plurafac RA340	—	—	—	73	—	—	0.977	—	0.974 at 25°C	–23	—	—
Renex 30	Colorless to pale yellow cloudy liquid	⩽1	14.5	75–85	—	—	1.0 at 25°C	⩽3.0	0.974 at 25°C	14	84	≈6.0 (1%)
Renex 31	Liquid	⩽1	15.4	60–74	—	—	1.0 at 25°C	⩽3.0	—	16	99	—
Renex 36	Colorless to pale yellow hazy liquid	⩽1	11.4	118–133	—	—	1.0 at 25°C	⩽1.0	>100	≈0.6	<0	≈6.0 (1%)
Ritoleth 2	Clear to slightly yellow liquid	<0.5	4.9	150–180	—	—	0.92 at 25°C	<1.0	149	—	—	—
Ritoleth 5	Clear to slightly yellow liquid	<2.0	8.8	120–133	—	—	0.94 at 25°C	<3.0	149	—	—	—
Ritoleth 10	White semi-solid paste	<10.0	12.3	80–90	32–40	<2.0	0.94 at 25°C	<3.0	149	—	47–55	4.5–7.5 (10%)
Ritoleth 20	White to light yellow liquid	—	—	—	—	—	1.01 at 25°C	—	149	—	—	—
Ritox 35	White waxy solid	—	—	—	—	—	1.05 at 25°C	—	—	—	—	—
Ritox 721	White waxy flakes	<2.0	—	44–61	—	—	1.02 at 25°C	<2.0	—	≈35°C	—	6.0–8.0 (0.5%)
Texofor A1P	Solid	—	16.2	—	—	—	1.025 at 60°C	—	—	40	>100	—
Texofor AP	—	—	—	—	—	—	0.875	—	—	31	Insoluble	—
Texofor A6	Solid	—	—	—	—	—	0.140	—	—	26	Insoluble	—
Texofor A10	Solid	—	—	—	—	—	0.970	—	—	30	75	—
Texofor A14	Solid	—	—	—	—	—	0.995	—	—	35	100	—
Texofor A30	Solid	—	—	—	—	—	1.035	—	—	43	>100	—
Texofor A45	Solid	—	—	—	—	—	1.055	—	—	47	>100	—
Texofor A60	Solid	—	—	—	—	—	1.065	—	—	48	>100	—
Volpo N 10	Hazy liquid	<2	—	79–91	31–37	—	—	<1.0	—	—	>55	—
Volpo N 20	Soft solid	<2	15.5	50–58	18–25	—	—	<1.0	—	—	>100	—
Volpo S2	White translucent plastic wax	<1	4.9	150–165	<2.0	<3.0	—	<1.0	—	41–45	—	6.0–7.5 (3%)
Volpo S10	White waxy solid	<1	12.4	78–86	<2.0	<3.0	—	<1.0	—	35–38	—	6.0–7.5 (3%)
Volpo S20	White to off- white waxy pastilles	<1	15.3	45–55	<2.0	<3.0	—	<1.0	—	42–48	—	6.0–7.5 (3%)
Volpo C2	White, waxy solid	<1	—	160–180	—	—	—	—	—	—	—	6.0–7.5 (3%)
Volpo C20	White, waxy solid	—	15.7	—	—	—	—	—	—	40–45	—	6.0–7.5 (3%)
Volpo CS10	White soft solid	—	—	—	—	—	—	—	—	35–38	—	6.0–7.5 (3%)
Volpo CS20	White waxy pastilles	<1	15.7	45–55	<2.0	<3.0	—	<1.0	—	44	—	6.0–7.5 (3%)
Volpo L4	Clear colorless liquid	<1	9.5	145–160	<2.0	<3.0	—	<1.0	—	—	—	—
Volpo L23	White waxy solid	<1	16.7	42–52	—	—	1.049 at 25°C	1–3	—	37	—	6.0–7.5 (3%)

Table IV: Typical properties of selected commercially available grades of polyoxyethylene alkyl ethers.

Name	Critical micelle concentration (%)	Surface tension of aqueous solution at 25°C (mN/m)			Dynamic viscosity at 25°C or pour point (mPa s)	Refractive index at 60°C	Solubility					
		(0.05%)	(0.1%)	(0.2%)			Ethanol	Fixed oils	Mineral oil	Propylene glycol	Water	Flash point (°C)
Brij 30	—	—	—	—	≈30	—	S	D	D	S	I	>149
Brij 35	0.013	—	—	—	—	—	S	I	I	S	S	>149
Brij 52	—	—	—	—	—	—	S	S	H	I	I	>149
Brij 56	—	—	—	—	—	—	H	D	I	D	H	>149
Brij 58	—	—	—	—	—	—	S	D	I	I	S	>149
Brij 72	—	—	—	—	—	—	S	S	I	I	I	>149
Brij 76	—	—	—	—	—	—	S	I	I	D	D	>149
Brij 78	—	—	—	—	—	—	S	D	I	I	D	>149
Brij 721	—	—	—	—	—	—	I	I	D	I	D	>110
Brij 93Veg	—	—	—	—	30	—	S	S	S	S	I	—
Brij 97	—	—	—	—	100	—	S	D	H	S	S	—
Brij 98	—	—	—	—	—	—	S	I	I	S	S	>149
Cremophor A6	—	—	—	—	13.5 at 60°C	1.4420–1.4424	S	I	—	—	S	190
Cremophor A20 polyether	—	—	—	—	—	—	—	—	—	—	D	>149
Cremophor A25	—	—	—	—	—	1.4512–1.4520	S	I	—	—	S	—
Ethosperse 1A4	—	—	—	—	30	—	S	S	—	—	S	—
Ethosperse 1A12	—	—	—	—	1000	—	S	SH	—	—	S	—
Ethosperse TDA6	—	—	—	—	80	—	S	I	—	—	D	—
Ethosperse S120	—	—	—	—	460	—	S	I	—	—	S	—
Ethosperse G26	—	—	—	—	150 at 38°C	—	S	I	—	—	S	—
Ethylan D252	—	—	—	—	—	—	—	—	—	—	I	—
Ethylan 253	—	—	—	—	—	—	—	—	—	—	I	—
Ethylan 254	—	—	—	—	—	—	—	—	—	—	I	—
Ethylan 256	—	—	—	—	—	—	—	—	—	—	S	—
Ethylan 257	—	—	—	—	—	—	—	—	—	—	S	—
Ethylan 2512	—	—	—	—	—	—	—	—	—	—	S	—
Ethylan 2560	—	—	—	—	—	—	—	—	—	—	S	—
Plurafac RA20	—	—	30.7	—	80	—	—	—	—	—	>10% at 25°C	246
Plurafac RA30	—	—	28.6	—	65	—	—	—	—	—	>10% at 25°C	235
Plurafac RA40	—	—	30.3	—	80	—	—	—	—	—	>10% at 25°C	256
Plurafac RA43	—	—	—	—	200	—	—	—	—	—	>1% at 25°C	225
Plurafac RA340	—	—	30.5	—	—	—	—	—	—	—	—	—
Renex 30	—	—	—	—	60	—	S	I	I	—	S	—
Renex 31	—	—	—	—	130	—	S	I	—	—	S	—
Renex 36	—	—	—	—	80	—	S	I	I	—	D	>93
Ritoleth 2	—	—	—	—	—	—	—	—	—	—	I	>149
Ritoleth 5	—	—	—	—	—	—	—	—	—	—	I	>149
Ritoleth 10	—	—	—	—	—	—	—	—	—	—	I	>149
Ritoleth 20	—	—	—	—	—	—	—	—	—	—	I	>149
Ritox 35	—	—	—	—	—	—	—	—	—	—	S	>149
Ritox 721	—	—	—	—	—	—	—	—	—	—	S	>149
Texofor A1P	0.006	42.9	—	42.3	—	—	S	—	—	—	S	—

Name	Critical micelle concentration (%)	Surface tension of aqueous solution at 25°C (mN/m)			Dynamic viscosity at 25°C or pour point (mPa s)	Refractive index at 60°C	Solubility					
		(0.05%)	(0.1%)	(0.2%)			Ethanol	Fixed oils	Mineral oil	Propylene glycol	Water	Flash point (°C)
Texofor AP	—	—	—	—	—	—	S	—	—	—	I	—
Texofor A6	—	—	—	—	—	—	S	—	—	—	I	—
Texofor A10	0.004	36.5	—	36.7	—	—	S	—	—	—	S	—
Texofor A14	—	36.9	—	36.6	—	—	S	—	—	—	S	—
Texofor A30	0.003	46.0	—	46.0	—	—	S	—	—	—	S	—
Texofor A45	0.004	47.5	—	47.0	—	—	S	—	—	—	S	—
Texofor A60	0.003	48.3	—	48.3	—	—	S	—	—	—	S	—
Volpo S2	—	—	—	—	—	—	S	—	—	—	D	>100
Volpo S10	—	—	—	—	—	—	S	—	—	—	S	>100
Volpo S20	—	—	—	—	—	—	S	—	—	—	S	>100
Volpo C2	—	—	—	—	—	—	S	—	—	—	D	>100
Volpo C20	—	—	—	—	—	—	S	—	—	—	S	>100
Volpo CS10	—	—	—	—	—	—	S	—	—	—	S	>100
Volpo CS20	—	—	—	—	—	—	S	—	—	—	S	>100
Volpo L4	—	—	—	—	—	—	S	—	—	—	S	—
Volpo L23	—	—	—	—	—	—	S	—	—	—	S	274

S = Soluble; H = Soluble with haze; I = Insoluble; D = Dispersible; SH = Soluble on heating.

Suppliers: ICI Surfactants (*Brij*, *Pharma* grades of *Brij 30, 35, 72, 76* and *78P* are also available); Croda Chemicals (*Volpo*); BASF Corporation (*Cremophor, Plurafac*); Rita Corporation (*Ritoleth, Ritox*).

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21 Authors

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Polyoxyethylene Castor Oil Derivatives

1 Nonproprietary Names

BP: Polyoxyl castor oil
Hydrogenated polyoxyl castor oil
PhEur: Macrogolglyceroli ricinoleas
Macrogolglyceroli hydroxystearas
USPNF: Polyoxyl 35 castor oil
Polyoxyl 40 hydrogenated castor oil

Polyoxyethylene castor oil derivatives are a series of materials obtained by reacting varying amounts of ethylene oxide with either castor oil or hydrogenated castor oil. Several different types of material are commercially available, the best-known being the *Cremophor* series (BASF Corp.). Of these, two castor oil derivatives are listed in the PhEur 2005 and USPNF 23.

See also Sections 2, 3 and 4.

2 Synonyms

Synonyms applicable to polyoxyethylene castor oil derivatives are shown below. *See* Table I for information on specific materials.

Acconon; *Arlatone*; *Cremophor*; *Etocas*; *Eumulgin*; *Jeechem*; *Lipocol*; *Mapeg*; *Marlowet*; *Nikkol*; *Protachem*; *Simulsol*.

3 Chemical Name and CAS Registry Number

Polyethoxylated castor oil [61791-12-6]

4 Empirical Formula and Molecular Weight

Polyoxyethylene castor oil derivatives are complex mixtures of various hydrophobic and hydrophilic components. Members within each range have different degrees of ethoxylation (moles)/PEG units as indicated by their numerical suffix (n). The chemical structures of the polyethoxylated hydrogenated castor oils are analogous to polyethoxylated castor oils with the exception that the double bond in the fatty chain has been saturated by hydrogenation.

The PhEur 2005 states that polyoxyl castor oil contains mainly ricinoleyl glycerol ethoxylated with 30–50 molecules of ethylene oxide (nominal value), with small amounts of macrogol ricinoleate, and of the corresponding free glycols. The PhEur 2005 also states that polyoxyl hydrogenated castor oil contains mainly trihydroxystearyl glycerol ethoxylated with 7–60 molecules of ethylene oxide (nominal value).

In polyoxyl 35 castor oil (*Cremophor EL*), the relatively hydrophobic constituents comprise about 83% of the total mixture, the main component being glycerol polyethylene glycol ricinoleate. Other hydrophobic constituents include fatty acid esters of polyethylene glycol along with some unchanged castor oil. The hydrophilic part (17%) consists of polyethylene glycols and glycerol ethoxylates. *Cremophor ELP*, a 'purified' grade of *Cremophor EL* is also a polyoxyl 35 castor oil; it has a lower content of water, potassium, and free fatty acids and hence is claimed to have improved stability.

In polyoxyl 40 hydrogenated castor oil (*Cremophor RH 40*), approximately 75% of the components of the mixture are hydrophobic. These comprise mainly fatty acid esters of

Table I: Synonyms of selected polyoxyethylene castor oil derivatives.

Name	Synonym
Polyoxyl 5 castor oil	*Acconon CA-5*; castor oil POE-5; *Etocas 5*; *Hetoxide C-5*; *Jeechem CA-5*; PEG-5 castor oil; polyoxyethylene 5 castor oil.
Polyoxyl 9 castor oil	*Acconon CA-9*; castor oil POE-9; *Jeechem CA-9*; PEG-9 castor oil; polyoxyethylene 9 castor oil; *Protachem CA-9*.
Polyoxyl 15 castor oil	*Acconon CA-15*; castor oil POE-15; *Jeechem CA-15*; PEG-15 castor oil; polyoxyethylene 15 castor oil; *Protachem CA-15*.
Polyoxyl 35 castor oil	Castor oil POE-35; *Cremophor EL*; *Cremophor ELP*; *Etocas 35*; glycerol polyethyleneglycol ricinoleate; PEG-35 castor oil; polyethoxylated castor oil; polyoxyethylene 35 castor oil.
Polyoxyl 40 castor oil	Castor oil POE-40; *Cirrasol G-1284*; *Croduret 40*; *Etocas 40*; *Eumulgin RO*; *Hetoxide C40*; *Jeechem CA-40*; *Marlowet R40*; *Nikkol CO 40TX*; *Nonionic GR-40*; PEG-40 castor oil; polyoxyethylene 40 castor oil; *Protachem CA-40*.
Polyoxyl 40 hydrogenated castor oil	*Cremophor RH 40*; *Croduret 40*; *Eumulgin HRE 40*; glycerol polyethyleneglycol oxystearate; *Hetoxide HC40*; hydrogenated castor oil POE-40; *Jeechem CAH-40*; PEG-40 hydrogenated castor oil; polyethoxylated hydrogenated castor oil; polyoxyethylene 40 hydrogenated castor oil; *Lipocol HCO-40*; *Lipocol LAV HCO 40*; *Nikkol HCO 40 Pharma*; *Nonionic GRH-40*; *Protachem CAH-40*.
Polyoxyl 60 castor oil	Castor oil POE-60;*Jeechem CA-60*; *Nikkol CO 60TX*; PEG-60 castor oil; polyoxyethylene 60 castor oil.
Polyoxyl 60 hydrogenated castor oil	*Croduret 60*; *Eumulgin HRE 60*; *Hetoxide HC60*; hydrogenated castor oil POE-60; *Jeechem CAH-60*; PEG-60 hydrogenated castor oil; polyoxyethylene 60 hydrogenated castor oil; *Lipocol HCO-60*; *Nikkol HCO 60 Pharma*; *Protachem CAH-60*.
Polyoxyl 100 castor oil	Hydrogenated castor oil POE-100; *Jeechem CA-100*; PEG-100 hydrogenated castor oil; polyoxyethylene 100 hydrogenated castor oil.
Polyoxyl 100 hydrogenated castor oil	*Cirrasol G-1300*; *Jeechem CA-100*; *Nikkol HCO 100*; polyoxyethylene 100 hydrogenated castor oil.
Polyoxyl 200 castor oil	*Hetoxide C200*; *Jeechem CA-200*; polyoxyethylene 200 castor oil; PEG-200 castor oil; castor oil POE-200.
Polyoxyl 200 hydrogenated castor oil	Hydrogenated castor oil POE-200; *Jeechem CAH-200*; PEG-200 hydrogenated castor oil; polyoxyethylene 200 hydrogenated castor oil.

glycerol polyethylene glycol and fatty acid esters of polyethylene glycol. The hydrophilic portion consists of polyethylene glycols and glycerol ethoxylates.

5 Structural Formula

See Section 4.

6 Functional Category

Emulsifying agent; solubilizing agent; wetting agent.

7 Applications in Pharmaceutical Formulation or Technology

Polyoxyethylene castor oil derivatives are nonionic surfactants used in oral, topical, and parenteral pharmaceutical formulations.

Polyoxyl 35 castor oil is mainly used as an emulsifing and solubilizing agent, and is particularly suitable for the production of aqueous liquid preparations containing volatile oils, fat-soluble vitamins, and other hydrophobic substances.(1,2) *Cremophor EL* emulsifies or solubilizes the fat-soluble vitamins A, D, E, and K in aqueous solutions for oral and topical administration. In 1 mL of a 25% v/v aqueous polyoxyl 35 castor oil (*Cremophor EL*) solution it is possible to incorporate approximately 10 mg of vitamin A palmitate; approximately 10 mg of vitamin D; approximately 120 mg of vitamin E acetate; or approximately 120 mg of vitamin K_1.

In aqueous alcoholic solutions, it very readily solubilizes essential oils. Aqueous solutions of hydrophobic drugs (e.g. miconazole, hexetidine, clotrimazole, benzocaine) can also be prepared with *Cremophor EL*. *Cremophor EL* has also been used as a solubilizing agent for drugs like cyclosporin A,(3) paclitaxel,(4) and cisplatin.(5) *Cremophor ELP* is manufactured by purifying *Cremophor EL* and is therefore suitable for parenteral applications, e.g. *Taxol* preparations. In oral formulations, the taste of polyoxyl 35 castor oil (*Cremophor EL*) can be masked by a banana flavor.

Polyoxyl 35 castor oil (*Cremophor EL*) has also been used as a solvent in proprietary injections of diazepam, propanidid, and alfaxalone with alfadolone acetate; *see* Section 14. A self-microemulsifying drug delivery system (SMEDDS) for oral bioavailability, and the enhancement of halofantrine,(6) and simvastatin,(7) has been prepared using *Cremophor EL*. *Cremophor EL* has also been used as a buffering agent for aqueous tropicamide eyedrops.(8) It has also been used in an aqueous mixture together with caprylic/capric glyceride for mucosal vaccination, providing a potential alternative to parenteral vaccination.(9) It has also been used to enhance the permeability of peptides across monolayers of Caco-2 cells by inhibiting the apically polarized efflux system, enhancing intestinal absorption of some drugs.(10) *Cremophor* has been used as a vehicle for boron neutron-capture therapy in mice; which is a form of radiation therapy used in the treatment of glioblastoma multiforme.(11) Polyoxyl 35 castor oil is also used in the production of glycerin suppositories.

In veterinary practice, polyoxyl 35 castor oil can be used to emulsify cod liver oil, and oils and fats incorporated into animal feeding stuffs.

In cosmetics, polyoxyl 35 castor oil is mainly used as a solubilizing agent for perfume bases and volatile oils in vehicles containing 30–50% v/v alcohol (ethanol or propan-2-ol). In hand lotions, it can be used to replace castor oil.

Polyoxyl 40 hydrogenated castor oil may be used in preference to polyoxyl 35 castor oil in oral formulations since it is almost tasteless. In aqueous alcoholic or completely aqueous solutions, polyoxyl 40 hydrogenated castor oil can be used to solubilize vitamins, essential oils, and certain drugs. Using 1 mL of a 25% v/v aqueous solution of polyoxyl 40 hydrogenated castor oil, it is possible to solubilize approximately 88 mg of vitamin A palmitate, or approximately 160 mg of vitamin A propionate. Other materials that can be solubilized are alfadolone, alfaxalone, hexachlorophene, hexetidine, levomepromazine, miconazole, propanidid, and thiopental.

In aerosol vehicles that include water, the addition of polyoxyl 40 hydrogenated castor oil improves the solubility of the propellant in the aqueous phase. This enhancement applies both to dichlorodifluoromethane and to propane/butane mixtures.

Foam formation in aqueous ethanol solutions containing polyoxyl 40 hydrogenated castor oil can be suppressed by the addition of small amounts of polypropylene glycol 2000.

Polyoxyl 40 hydrogenated castor oil is also used as an emulsifier of fatty acids and alcohols.

Polyoxyethylene castor oil derivatives have been used experimentally as a surfactant for the controlled release matrix pellet formulation containing nanocrystalline ketoprofen,(12) and for the transdermal delivery of vinpocetin.(13)

Hydrogenated castor oil (HCO) derivatives containing more than 20 oxyethylene units were found to prolong the plasma circulation times of menatetrenone incorporated in lipid emulsions.(14) Polyoxl 60 hydrogenated castor oil has been reported to provide a self-microemulsifying system with enhanced oral absorption,(15) and a drastic reduction in plasma clearance of lipid emulsions.(16) It has been used in the formulation of liposomes,(17) and it has been suggested that more than 60% aids in the targeting of liposomes to the liver.(18) Also, polyoxyl 60 hydrogenated castor oil micellar solutions of cyclosporin A delivered the drug via the GI tract to the lymphatics with an extremely high selectivity.(19,20)

Cremophor RH 40 and *RH 60* have been used as additives to enhance the drug release from suppository formulations.(21,22)

8 Description

Polyoxyl 35 castor oil occurs as a pale yellow, viscous liquid that is clear at temperatures above 26°C. It has a slight but characteristic odor and can be completely liquefied by heating to 26°C.

Polyoxyl 40 hydrogenated castor oil occurs as a white to yellowish, semisolid paste at 20°C that liquefies at 30°C. It has a very faint characteristic odor and is almost tasteless in aqueous solution.

Polyoxyl 60 hydrogenated castor oil occurs as a white paste at room temperature. It has little taste or odor in aqueous solution.

9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

See Tables III, IV, and V.

11 Stability and Storage Conditions

Polyoxyl 35 castor oil (*Cremophor EL* and *Cremophor ELP*) forms stable solutions in many organic solvents such as

Table II: Pharmacopeial specifications for polyoxyethylene castor oil derivatives.

Test	PhEur 2005		USPNF 23	
	Polyoxyl castor oil	**Polyoxyl hydrogenated castor oil**	**Polyoxyl 35 castor oil**	**Polyoxyl 40 hydrogenated castor oil**
Identification	+	+	+	+
Characters	+	+	—	—
Appearance of solution	+	+	—	—
Alkalinity	+	+	—	—
Relative density	≈1.05	—	—	—
Specific gravity	—	—	1.05–1.06	—
Congealing temperature	—	—	—	16–26°C
Viscosity at 25°C	500–800 mPa s	—	650–850 cP s	—
Water	⩽3.0%	⩽3.0%	⩽3.0%	⩽3.0%
Total ash	⩽0.3%	⩽0.3%	—	—
Residue on ignition	—	—	⩽0.3%	⩽0.3%
Heavy metals	⩽10 ppm	⩽10 ppm	⩽0.001%	⩽0.001%
Acid value	⩽2.0	⩽2.0	⩽2.0	⩽2.0
Hydroxyl value	+	+	65–80	60–80
Dioxan	⩽10 ppm	⩽10 ppm	—	—
Free ethylene oxide	⩽1 ppm	⩽1 ppm	—	—
Organic volatile impurities	—	—	+	+

chloroform, ethanol, and propan-2-ol; it also forms clear, stable, aqueous solutions. Polyoxyl 35 castor oil (*Cremophor EL* and *Cremophor ELP*) is miscible with other polyoxyethylene castor oil derivatives and on heating with fatty acids, fatty alcohols, and some animal and vegetable oils. Solutions of polyoxyl 40 hydrogenated castor oil (*Cremophor RH 40*) in aqueous alcohols are also stable.

On heating of an aqueous solution, the solubility of polyoxyl 35 castor oil (*Cremophor EL* and *Cremophor ELP*) is reduced and the solution becomes turbid. Aqueous solutions of polyoxyl hydrogenated castor oil (*Cremophor RH* grades) heated for prolonged periods may separate into solid and liquid phases on cooling. However, the product can be restored to its original form by homogenization.

Aqueous solutions of polyoxyl 35 castor oil (*Cremophor EL* and *Cremophor ELP*) are stable in the presence of low concentrations of electrolytes such as acids or salts, with the exception of mercuric chloride; *see* Section 12.

Aqueous solutions of polyoxyl 35 castor oil (*Cremophor EL* and *Cremophor ELP*) can be sterilized by autoclaving for 20 minutes at 121°C. In this process, a product may acquire a deeper color but this has no significance for product stability. Aqueous solutions of polyoxyl hydrogenated castor oil (*Cremophor RH*) can similarly be sterilized by autoclaving at 121°C, but this may cause a slight decrease in the pH value.

Although the method of manufacture used for polyoxyethylene castor oil derivatives ensures that they are near-sterile, microbial contamination can occur on storage.

Polyoxyethylene castor oil derivatives should be stored in a well-filled, airtight container, protected from light, in a cool, dry place.

12 Incompatibilities

In strongly acidic or alkaline solutions, the ester components of polyoxyethylene hydrogenated castor oil are liable to saponify.

In aqueous solution, polyoxyl 35 castor oil (*Cremophor EL* and *Cremophor ELP*) is stable toward most electrolytes in the concentrations normally employed. However, it is incompatible with mercuric chloride since precipitation occurs.

Some organic substances may cause precipitation at certain concentrations, especially compounds containing phenolic hydroxyl groups, e.g. phenol, resorcinol, and tannins.

Polyoxyl 40 hydrogenated castor oil (*Cremophor RH 40*) and polyoxyl 60 hydrogenated castor oil are largely unaffected by the salts that cause hardness in water. *Cremophor RH 40* was found to prolong the dissolution time of digoxin tablets.(23)

13 Method of Manufacture

Polyoxyethylene castor oil derivatives are prepared by reacting varying amounts of ethylene oxide with either castor oil or hydrogenated castor oil under controlled conditions.

Polyoxyl 35 castor oil is produced in this way by reacting 1 mole of castor oil with 35–40 moles of ethylene oxide.

Polyoxyl 40 hydrogenated castor oil is produced by reacting 1 mole of hydrogenated castor oil with 40–45 moles of ethylene oxide. Polyoxyl 60 hydrogenated castor oil is similarly produced by reacting 1 mole of hydrogenated castor oil with 60 moles of ethylene oxide.

14 Safety

Polyoxyethylene castor oil derivatives are used in a variety of oral, topical, and parenteral pharmaceutical formulations.

Acute and chronic toxicity tests in animals have shown polyoxyethylene castor oil derivatives to be essentially nontoxic and nonirritant materials; *see* Table VI.(24,25) However, there are reports of cardiovascular changes and nephrotoxicity in various species of animals.(26) Several serious anaphylactic reactions,(27–38) cardiotoxicity,(39–41) nephrotoxicity,(42,43) neurotoxicity,(44) and pulmonary toxicty(45) have also been observed in humans and animals following parenteral administration of formulations containing polyoxyethylene castor oil derivatives. The precise mechanism of the reaction is not known.

Table III: Typical physical properties of selected commercially available polyoxyethylene castor oil derivatives.

Name	Acid value	HLB value	Hydroxyl value	Iodine number	Saponification value	Water content (%)	Melting point (°C)	Solidification point (°C)	Cloud point for a 1% aqueous solution (°C)
Polyoxyl 35 castor oil (*Cremophor EL*)	⩽2.0	12–14	65–78	25–35	65–70	2.80	19–20	—	72.5
Poloxyl 35 castor oil, purified (*Cremophor ELP*)	⩽2.0	12–14	65–78	25–35	65–70	⩽0.5	—	—	—
Polyoxyl 40 hydrogenated castor oil (*Cremophor RH 40*)	⩽1.0	14–16	60–80	⩽1	50–60	⩽2.0	≈30	20–28	95.6
Polyoxyl 60 hydrogenated castor oil	⩽1.0	15–17	50–70	⩽1	40–50	⩽2	≈40	—	—
Etocas 29	—	11.7	—	—	—	—	—	—	—
Etocas 35	—	12.7	—	—	—	—	—	—	—
Etocas 40	—	13	—	—	—	—	—	—	—
Croduret 7 Special	—	4.9	—	—	—	—	—	—	—
Croduret 40	—	13	—	—	—	—	—	—	—
Croduret 50 Special	—	14.1	—	—	—	—	—	—	—
Croduret 60	—	14.7	—	—	—	—	—	—	—
Eumulgin HRE 40	⩽1.0	—	60–75	⩽2	50–60	⩽1.0	—	—	76–82
Eumulgin HRE 60	⩽1.0	—	50–67	—	40–50	⩽1	—	<22	80–86
Arlatone G Pharma	—	10.8	—	—	—	—	≈7	—	—
Cirrasol G-1284	—	13.1	—	—	—	—	—	—	—
Hetoxide C5	—	4	—	—	—	—	—	—	—
Hetoxide C-16	—	8.6	—	—	—	—	—	—	—
Hetoxide C-25	—	10.8	—	—	—	—	—	—	—
Hetoxide HC-16	—	8.6	—	—	—	—	—	—	—
Hetoxide HC-40	—	13.1	—	—	—	—	—	—	—
Hetoxide HC-60	—	14.8	—	—	—	—	—	—	—
Jeechem CA-5	⩽1.5	—	128–140	63–73	138–153	⩽1.0	—	—	—
Jeechem CA-15	⩽1.0	—	—	—	95–100	⩽1.0	—	—	—
Jeechem CA-25	—	—	75–85	—	77–85	⩽1.0	—	—	—
Jeechem CA-40	⩽2.0	—	77–89	24–30	57–64	⩽3.0	—	—	—
Jeechem CA-60	⩽2.0	—	42–55	—	28–38	⩽12.0	—	—	—
Jeechem CA-100	⩽2.0	—	—	—	27–37	⩽1.0	—	—	—
Jeechem CA-200	⩽2.0	—	20–34	—	14–20	⩽1.0	125	—	—
Jeechem CAH-25	⩽2.0	—	73–84	⩽1.0	77–87	⩽2.0	—	—	—
Jeechem CAH-40	⩽3.0	—	59–68	⩽2.0	50–65	⩽1.0	—	—	—
Jeechem CAH-60	⩽1.5	—	39–49	—	41–51	⩽1.0	—	—	—
Jeechem CAH-200	⩽2.0	—	20–33	—	14–22	⩽1.0	125	—	—
Lipocol HCO-40	⩽3.0	—	—	⩽2.0	60–67	—	—	—	—
Lipocol LAV HCO-40	⩽1.0	—	60–80	⩽2.0	45–69	⩽3.0	—	—	—
Lipocol HCO-60	⩽1.0	—	50–70	⩽1.0	40–50	⩽21.0	—	—	—
Nikkol CO-3	—	3	—	—	—	—	—	—	—
Nikkol CO-10	—	6.5	—	—	—	—	—	—	—
Nikkol HCO-50	—	13.5	—	—	—	—	—	—	—
Nikkol HCO-80	—	15	—	—	—	—	—	—	—
Nikkol HCO-100	—	16.5	—	—	—	—	—	—	—

Table IV: Typical physical properties of selected commercially available polyoxyethylene castor oil derivatives.

Name	Density (g/cm^3)	pH	Refractive index at 20°C	Surface tension of 0.1% w/v aqueous solution (mN/m)	Viscosity at 25°C (mPa s)	Critical micelle concentration (%)
Polyoxyl 35 castor oil (*Cremophor EL*)	1.05–1.06	6–8	1.471	40.9	650–800	≈0.009
Poloxyl 35 castor oil, purified (*Cremophor ELP*)	1.05–1.06	5–7	—	—	600–750	≈0.009
Polyoxyl 40 hydrogenated castor oil (*Cremophor RH 40*)	—	6–7	1.453–1.457	43.0	20–40[a]	0.039
Polyoxyl 60 hydrogenated castor oil	—	6–7	—	—	—	—
Eumulgin HRE 40	1.0220–1.0260 at 70°C	6–7	—	—	—	—
Eumulgin HRE 60	1.0340–1.0380 at 70°C	6–7	—	—	—	—
Arlacel 989	—	—	—	—	1200	—
Arlatone G Pharma	≈1.0	—	—	—	≈1400	—
Cirrasol G-1284	≈1.10	7–9	—	—	1500	—
Jeechem CA-5	1.0	6–8	—	—	—	—
Jeechem CA-9	1.02	5.5–7.5	—	—	—	—
Jeechem CA-15	1.021	6.0–7.5	—	—	—	—
Jeechem CA-25	1.04	6.0–7.5	—	—	—	—
Jeechem CA-30	1.01	6.5–7.5	—	—	—	—
Jeechem CA-40	1.1	5.0–8.0	—	—	—	—
Jeechem CA-60	1.068	5.0–7.0	—	—	—	—
Jeechem CA-100	—	5.5–7.0	—	—	—	—
Jeechem CA-200	1.08	5.0–7.0	—	—	—	—
Jeechem CAH-16	1.02	6.0–7.5	1.4665–1.4685	—	—	—
Jeechem CAH-25	1.03	5.0–7.5	—	—	—	—
Jeechem CAH-40	1.1	5.5–7.5	—	—	—	—
Jeechem CAH-60	—	3.5–6.1	—	—	—	—
Jeechem CAH-100	1.1	3.5–6.1	—	—	—	—
Jeechem CAH-200	1.1	—	—	—	—	—
Lipocol HCO-40	1.0	—	—	—	—	—
Lipocol HCO-60	1.05	—	—	—	—	—

(a) 30% w/v aqueous solution.

Table V: Solubility of selected commercially available polyoxyethylene castor oil derivatives.

Name	Solubility							
	Castor oil	Chloroform	Ethanol	Fatty acids	Fatty alcohols	Olive oil	Mineral oil	Water
Polyoxyl 35 castor oil (*Cremophor EL*)	S	S	S	S	S	S	—	S
Poloxyl 35 castor oil, purified (*Cremophor ELP*)	S	S	S	S	S	S	—	S
Polyoxyl 40 hydrogenated castor oil (*Cremophor RH 40*)	S	S	S	S	S	S	—	S
Polyoxyl 60 hydrogenated castor oil	S	—	S[a]	S	S	S	—	S
Etocas 5	S	—	S	—	S	—	I	I
Etocas 29	S	—	S	—	S	—	I	S
Etocas 35	S	—	S	—	S	—	I	S
Etocas 40	S	—	S	—	PS	—	I	S
Croduret 7 Special	S	—	PS	—	S	—	I	I
Croduret 40	D	—	S	—	D	—	I	S
Croduret 50 Special	D	—	S	—	I	—	I	S
Croduret 60	D	—	S	—	D	—	I	S
Arlacet 989	—	—	S	—	—	—	—	I
Arlatone G Pharma	—	—	S	—	—	—	I	S
Cirrasol G-1284	—	—	—	—	—	—	I	D
Jeechem CA-5	—	—	—	—	—	—	—	D
Jeechem CA-9	—	—	—	—	—	—	—	D
Jeechem CA-15	—	—	—	—	—	—	—	PS
Jeechem CA-25	—	—	—	—	—	—	—	S
Jeechem CA-30	—	—	—	—	—	—	—	S
Jeechem CA-40	—	—	—	—	—	—	—	S
Jeechem CA-60	—	—	—	—	—	—	—	PS
Jeechem CA-200	—	—	—	—	—	—	—	S
Jeechem CAH-16	—	—	—	—	—	—	—	D
Jeechem CAH-25	—	—	—	—	—	—	—	D
Jeechem CAH-40	—	—	—	—	—	—	—	S
Jeechem CAH-60	—	—	—	—	—	—	—	S
Jeechem CAH-100	—	—	—	—	—	—	—	S
Jeechem CAH-200	—	—	—	—	—	—	—	S
Lipocol LAV HCO-40	—	—	—	—	—	—	—	S
Lipocol HCO-40	—	—	—	—	—	—	—	S
Lipocol HCO-60	—	—	—	—	—	—	—	S

S = soluble, PS = partially soluble, I = insoluble, D = dispersible.

[a] Need to add 0.5–1.0% water to maintain a clear solution.

Table VI: LD_{50} values of selected polyoxyethylene castor oil derivatives.[24,25]

Name	Animal and route	LD_{50} (g/kg body-weight)
Polyoxyl 35 castor oil (*Cremophor EL*)	Cat (oral)	>10
	Dog (IV)	0.64
	Mouse (IV)	2.5
	Rabbit (oral)	>10
	Rat (oral)	>6.4
Polyoxyl 40 hydrogenated castor oil (*Cremophor RH 40*)	Mouse (IP)	>12.5
	Mouse (IV)	>12.0
	Rat (oral)	>16.0
Polyoxyl 60 hydrogenated castor oil	Mouse (IP)	>12.5
	Rat (oral)	>16.0

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IV injections and ophthalmic solutions). Included in parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Polyoxyethylene alkyl ethers; polyoxyethylene stearates.

18 Comments

Note that the trade name *Cremophor* (BASF Corp.) is also used for other polyoxyethylene derivatives, e.g., the *Cremophor A* series are polyoxyethylene alkyl ethers of cetostearyl alcohol.

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22 Date of Revision

30 August 2005.

Polyoxyethylene Sorbitan Fatty Acid Esters

1 Nonproprietary Names

BP:	Polysorbate 20, Polysorbate 40, Polysorbate 60, and Polysorbate 80
JP:	Polysorbate 80
PhEur:	Polysorbatum 20, Polysorbatum 40, Polysorbatum 60, and Polysorbatum 80
USPNF:	Polysorbate 20, Polysorbate 40, Polysorbate 60, and Polysorbate 80

2 Synonyms

For synonyms of selected polysorbates, *see* Table I; *see also* Section 3.

3 Chemical Names and CAS Registry Numbers

See Table II.

4 Empirical Formula and Molecular Weight

Approximate molecular weights for selected polysorbates are shown in Table III.

Table II: Chemical names and CAS Registry Numbers of selected polysorbates.

Polysorbate	Chemical name	CAS number
Polysorbate 20	Polyoxyethylene 20 sorbitan monolaurate	[9005-64-5]
Polysorbate 21	Polyoxyethylene (4) sorbitan monolaurate	[9005-64-5]
Polysorbate 40	Polyoxyethylene 20 sorbitan monopalmitate	[9005-66-7]
Polysorbate 60	Polyoxyethylene 20 sorbitan monostearate	[9005-67-8]
Polysorbate 61	Polyoxyethylene (4) sorbitan monostearate	[9005-67-8]
Polysorbate 65	Polyoxyethylene 20 sorbitan tristearate	[9005-71-4]
Polysorbate 80	Polyoxyethylene 20 sorbitan monooleate	[9005-65-6]
Polysorbate 81	Polyoxyethylene (5) sorbitan monooleate	[9005-65-6]
Polysorbate 85	Polyoxyethylene 20 sorbitan trioleate	[9005-70-3]
Polysorbate 120	Polyoxyethylene 20 sorbitan monoisostearate	[66794-58-9]

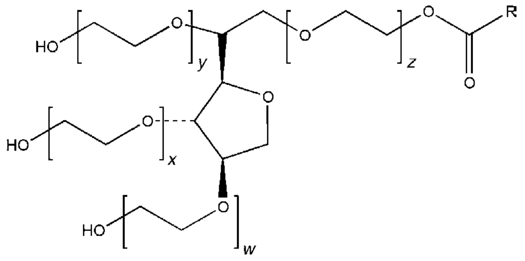
Table I: Synonyms of selected polysorbates.

Polysorbate	Synonym
Polysorbate 20	*Armotan PML 20*; *Capmul POE-L*; *Campul POE-L Low PV*; *Crillet 1*; *Drewmulse*; E432; *Durfax 20*; E432; *Eumulgin SML*; *Glycosperse L-20*; *Hodag PSML-20*; *Lamesorb SML-20*; *Liposorb L-20*; *Liposorb L-20K*; *Montanox 20*; *Nissan Nonion LT-221*; *Norfox Sorbo T-20*; *POE-SML*; *Ritabate 20*; *Sorbax PML-20*; sorbitan monododecanoate; *Sorgen TW-20*; *T-Maz 20*; *T-Maz 20K*; poly(oxy-1,2-ethanediyl) derivatives; polyoxyethylene 20 laurate; *Protasorb L-20*; *Tego SML 20*; *Tween 20*.
Polysorbate 21	*Crillet 11*; *Hodag PSML-4*; *Protasorb L-5*; *Tween 21*.
Polysorbate 40	*Crillet 2*; E434; *Eumulgin SMP; Glycosperse S-20*; *Hodag PSMP-20*; *Lamesorb SMP-20; Liposorb P-20; Lonzest SMP-20; Montanox 40*; poly(oxy-1,2-ethanediyl) derivatives; *Protasorb P-20*; *Ritabate 40*; sorbitan monohexadecanoate; *Sorbax PMP-20; Tween 40.*
Polysorbate 60	*Atlas 70K; Atlas Armotan PMS 20*; *Capmul POE-S; Cremophor PS 60; Crillet 3*; *Drewpone 60K; Durfax 60; Durfax 60K;* E435; *Emrite 6125; Eumulgin SMS; Glycosperse S-20; Glycosperse S-20FG; Glycosperse S-20FKG; Hodag PSMS-20; Hodag SVS-18; Lamsorb SMS-20; Liposorb S-20; Liposorb S-20K; Lonzest SMS-20; Nikkol TS-10; Norfox SorboT-60 Montanox 60; Polycon T 60 K*; polyoxyethylene 20 stearate; *Ritabate 60; Protasorb S-20; Sorbax PMS-20;* sorbitan monooctadecanoate poly(oxy-1,2-ethanediyl) derivatives; *T-Maz 60; T-Max 60KHS; Tween 60; Tween 60K; Tween 60 VS.*
Polysorbate 61	*Crillet 31*; *Hodag PSMS-4*; *Liposorb S-4*; *Protasorb S-4*; *Tween 61*.
Polysorbate 65	*Alkamuls PSTS-20; Crillet 35*; E436; *Glycosperse TS-20; Glycosperse TS-20 FG; Glycosperse TS-20 KFG; Hodag PSTS-20; Lamesorb STS-20; Lanzet STS-20; Liposorb TS-20; Liposorb TS-20A; Liposorb TS-20K; Montanox 65*; *Protasorb STS-20; Sorbax PTS-20;* sorbitan trioctadecanoate poly(oxy-1,2-ethanediyl) derivatives; *T-Maz 65K; Tween 65; Tween 65K; Tween 65V.*
Polysorbate 80	*Atlas E; Armotan PMO 20*; *Capmul POE-O; Cremophor PS 80; Crillet 4*; *Crillet 50*; *Drewmulse POE-SMO; Drewpone 80K; Durfax 80; Durfax 80K;* E433; *Emrite 6120; Eumulgin SMO; Glycosperse O-20*; *Hodag PSMO-20*; *Liposorb O-20*; *Liposorb O-20K; Montanox 80*; polyoxyethylene 20 oleate; *Protasorb O-20*; *Ritabate 80*; (*Z*)-sorbitan mono-9-octadecenoate poly(oxy1,2-ethanediyl) derivatives; *Tego SMO 80; Tego SMO 80V; Tween 80.*
Polysorbate 81	*Crillet 41*; *Hetsorb O-5; Hodag PSMO-5; Protasorb O-5; Sorbax PMO-5;* sorbitan mono-9-octadecenoate poly(oxy-1,2-ethanediyl) derivatives; *T-Maz 81; Tego SMO 81; Tween 81.*
Polysorbate 85	*Alkamuls PSTO-20; Crillet 45*; *Glycosperse TO-20; Hodag PSTO-20; Lonzest STO-20; Liposorb TO-20; Montanox 85; Protasorb TO-20; Sorbax PTO-20;* sorbitan tri-9-octadecenoate poly(oxy1,2-ethanediyl) derivatives; *Tego STO 85; Tween 85.*
Polysorbate 120	*Crillet 6.*

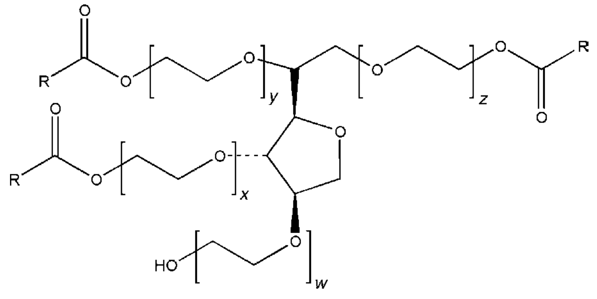
Table III: Empirical formula and molecular weight of selected polysorbates.

Polysorbate	Formula	Molecular weight
Polysorbate 20	$C_{58}H_{114}O_{26}$	1128
Polysorbate 21	$C_{26}H_{50}O_{10}$	523
Polysorbate 40	$C_{62}H_{122}O_{26}$	1284
Polysorbate 60	$C_{64}H_{126}O_{26}$	1312
Polysorbate 61	$C_{32}H_{62}O_{10}$	607
Polysorbate 65	$C_{100}H_{194}O_{28}$	1845
Polysorbate 80	$C_{64}H_{124}O_{26}$	1310
Polysorbate 81	$C_{34}H_{64}O_{11}$	649
Polysorbate 85	$C_{100}H_{188}O_{28}$	1839
Polysorbate 120	$C_{64}H_{126}O_{26}$	1312

5 Structural Formula



Polyoxyethylene sorbitan monoester



Polyoxyethylene sorbitan triester

$w + x + y + z = 20$ (Polysorbates 20, 40, 60, 65, 80, and 85)
$w + x + y + z = 5$ (Polysorbates 81)
$w + x + y + z = 4$ (Polysorbates 21 and 61)
R = fatty acid

6 Functional Category

Emulsifying agent; nonionic surfactant; solubilizing agent; wetting, dispersing/suspending agent.

7 Applications in Pharmaceutical Formulation or Technology

Polyoxyethylene sorbitan fatty acid esters (polysorbates) are a series of partial fatty acid esters of sorbitol and its anhydrides copolymerized with approximately 20, 5, or 4 moles of ethylene oxide for each mole of sorbitol and its anhydrides. The resulting product is therefore a mixture of molecules of varying sizes rather than a single uniform compound.

Polysorbates containing 20 units of oxyethylene are hydrophilic nonionic surfactants that are used widely as emulsifying agents in the preparation of stable oil-in-water pharmaceutical emulsions. They may also be used as solubilizing agents for a variety of substances including essential oils and oil-soluble vitamins, and as wetting agents in the formulation of oral and parenteral suspensions. They have been found to be useful in improving the oral bioavailability of drug molecules that are substrates for *p*-glycoprotein.(1)

Polysorbates are also widely used in cosmetics and food products. *See* Table IV.

Table IV: Uses of polysorbates.

Use	Concentration (%)
Emulsifying agent	
Used alone in oil-in-water emulsions	1–15
Used in combination with hydrophilic emulsifiers in oil-in-water emulsions	1–10
Used to increase the water-holding properties of ointments	1–10
Solubilizing agent	
For poorly soluble active constituents in lipophilic bases	1–10
Wetting agent	
For insoluble active constituents in lipophilic bases	0.1–3

8 Description

Polysorbates have a characteristic odor and a warm, somewhat bitter taste. Their colors and physical forms at 25°C are shown in Table V, although it should be noted that the absolute color intensity of the products may vary from batch to batch and from manufacturer to manufacturer.

Table V: Colors and physical forms of selected polysorbates at 25°C.

Polysorbate	Color and form at 25°C
Polysorbate 20	Yellow oily liquid
Polysorbate 21	Yellow oily liquid
Polysorbate 40	Yellow oily liquid
Polysorbate 60	Yellow oily liquid
Polysorbate 61	Tan solid
Polysorbate 65	Tan solid
Polysorbate 80	Yellow oily liquid
Polysorbate 81	Amber liquid
Polysorbate 85	Amber liquid
Polysorbate 120	Yellow liquid

9 Pharmacopeial Specifications

See Table VI.

Table VI: Pharmacopeial specifications for polysorbates.

Test	JP 2001	PhEur 2005	USPNF 23
Identification			
Polysorbate 20	—	+	+
Polysorbate 40	—	+	+
Polysorbate 60	—	+	+
Polysorbate 80	+	+	+
Saponification value			
Polysorbate 20	—	40–50	40–50
Polysorbate 40	—	41–52	41–52
Polysorbate 60	—	45–55	45–55
Polysorbate 80	45–55	45–55	45–55
Composition of fatty acids	—	*see* Table VII	—
Hydroxyl value			
Polysorbate 20	—	96–108	96–108
Polysorbate 40	—	89–105	89–105
Polysorbate 60	—	81–96	81–96
Polysorbate 80	—	65–80	65–80
Water			
Polysorbate 20	—	⩽3.0%	⩽3.0%
Polysorbate 40	—	⩽3.0%	⩽3.0%
Polysorbate 60	—	⩽3.0%	⩽3.0%
Polysorbate 80	⩽3.0%	⩽3.0%	⩽3.0%
Residue on ignition			
Polysorbate 20	—	⩽0.25%	⩽0.25%
Polysorbate 40	—	⩽0.25%	⩽0.25%
Polysorbate 60	—	⩽0.25%	⩽0.25%
Polysorbate 80	⩽0.15%	⩽0.25%	⩽0.25%
Arsenic			
Polysorbate 80	⩽2 ppm	—	—
Heavy metals			
Polysorbate 20	—	⩽10 ppm	⩽0.001%
Polysorbate 40	—	⩽10 ppm	⩽0.001%
Polysorbate 60	—	⩽10 ppm	⩽0.001%
Polysorbate 80	⩽20 ppm	⩽10 ppm	⩽0.001%
Acid value			
Polysorbate 20	—	⩽2.0	⩽2.2
Polysorbate 40	—	⩽2.0	⩽2.2
Polysorbate 60	—	⩽2.0	⩽2.2
Polysorbate 80	⩽2.0	⩽2.0	⩽2.2
Iodine value			
Polysorbate 80	19–24	—	—
Specific gravity			
Polysorbate 20	—	≈1.10	—
Polysorbate 40	—	≈1.10	—
Polysorbate 60	—	≈1.10	—
Polysorbate 80	1.065–1.095	≈1.10	1.06–1.09
Viscosity at 25°C			
Polysorbate 20	—	≈400 mPa s	—
Polysorbate 40	—	≈400 mPa s	—
Polysorbate 60	—	≈400 mPa s	—
Polysorbate 80	345–445 mm^2	≈400 mPa s	300–500 mm^2/s
Organic volatile impurities	—	—	+
Peroxide value			
Polysorbate 20	—	⩽10	—
Polysorbate 40	—	⩽10	—
Polysorbate 60	—	⩽10	—
Polysorbate 80	—	⩽10	—
Residual ethylene oxide			
Polysorbate 20	—	⩽1 ppm	—
Polysorbate 40	—	⩽1 ppm	—
Polysorbate 60	—	⩽1 ppm	—
Polysorbate 80	—	⩽1 ppm	—
Residual dioxan			

Continued

Table VI: Continued

Test	JP 2001	PhEur 2005	USPNF 23
Polysorbate 20	—	⩽10 ppm	—
Polysorbate 40	—	⩽10 ppm	—
Polysorbate 60	—	⩽10 ppm	—
Polysorbate 80	—	⩽10 ppm	—

Table VII: Fatty acid composition of polysorbate 20, 40, 60, 80 from PhEur 2005.

Fatty acid	Polysorbate 20	Polysorbate 40	Polysorbate 60	Polysorbate 80
Caproic acid	⩽1.0%	—	—	—
Caprylic acid	⩽10.0%	—	—	—
Capric acid	⩽10.0%	—	—	—
Lauric acid	40.0–60.0%	—	—	—
Myristic acid	14.0–25.0%	—	—	⩽5.0%
Palmitic acid	7.0–15.0%	⩾92.0%	+(a)	⩽16.0%
Palmitoleic acid	—	—	—	⩽8.0%
Stearic acid	⩽7.0%	—	40.0–60.0%	⩽6.0%
Oleic acid	⩽11.0%	—	—	58.0–85.0%
Linolenic acid	—	—	—	⩽4.0%
Linoleic acid	⩽3.0%	—	—	—

(a) Sum of the contents of palmitic and stearic acids ⩾90.0%.

10 Typical Properties

Acid value: *see* Table VIII.
Acidity/alkalinity: pH = 6.0–8.0 for a 5% w/v aqueous solution.
Flash point: 149°C
HLB value: *see* Table IX.
Hydroxyl value: *see* Table VIII.
Moisture content: *see* Table VIII.
Saponification value: *see* Table VIII.
Solubility: *see* Table X.
Specific gravity: *see* Table IX.
Surface tension: for 0.1% w/v solutions, *see* Table XI.
Viscosity (dynamic): *see* Table IX.

Table VIII: Typical properties of selected polysorbates.

Polysorbate	Acid value (%)	Hydroxyl value	Moisture content	Saponification value
Polysorbate 20	2.0	96–108	3.0	40–50
Polysorbate 21	3.0	225–255	3.0	100–115
Polysorbate 40	2.0	90–105	3.0	41–52
Polysorbate 60	2.0	81–96	3.0	45–55
Polysorbate 61	2.0	170–200	3.0	95–115
Polysorbate 65	2.0	44–60	3.0	88–98
Polysorbate 80	2.0	65–80	3.0	45–55
Polysorbate 81	2.0	134–150	3.0	96–104
Polysorbate 85	2.0	39–52	3.0	80–95
Polysorbate 120	2.0	65–85	5.0	40–50

Table IX: Typical properties of selected polysorbates.

Polysorbate	HLB value	Specific gravity at 25°C	Viscosity (mPa s)
Polysorbate 20	16.7	1.1	400
Polysorbate 21	13.3	1.1	500
Polysorbate 40	15.6	1.08	500
Polysorbate 60	14.9	1.1	600
Polysorbate 61	9.6	1.06	Solid
Polysorbate 65	10.5	1.05	Solid
Polysorbate 80	15.0	1.08	425
Polysorbate 81	10.0	—	450
Polysorbate 85	11.0	1.00	300
Polysorbate 120	14.9	—	—

Table X: Solubilities of selected polysorbates in various solvents.

Polysorbate	Solvent			
	Ethanol	Mineral oil	Vegetable oil	Water
Polysorbate 20	S	I	I	S
Polysorbate 21	S	I	I	D
Polysorbate 40	S	I	I	S
Polysorbate 60	S	I	I	S
Polysorbate 61	SW	SW	SWT	D
Polysorbate 65	SW	SW	DW	D
Polysorbate 80	S	I	I	S
Polysorbate 81	S	S	ST	D
Polysorbate 85	S	I	ST	D
Polysorbate 120	S	I	I	S

D = dispersible; I = insoluble; S = soluble; T = turbid; W = on warming.

Table XI: Surface tension of related polysorbates.

Polysorbate	Surface tension at 20°C (mN/m)
Polysorbate 21	34.7
Polysorbate 40	41.5
Polysorbate 60	42.5
Polysorbate 61	41.5
Polysorbate 80	42.5
Polysorbate 85	41.0

11 Stability and Storage Conditions

Polysorbates are stable to electrolytes and weak acids and bases; gradual saponification occurs with strong acids and bases. The oleic acid esters are sensitive to oxidation. Polysorbates are hygroscopic and should be examined for water content prior to use and dried if necessary. Also, in common with other polyoxyethylene surfactants, prolonged storage can lead to the formation of peroxides.

Polysorbates should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

Discoloration and/or precipitation occur with various substances, especially phenols, tannins, tars, and tarlike materials. The antimicrobial activity of paraben preservatives is reduced in the presence of polysorbates.(2) *See* Methylparaben.

13 Method of Manufacture

Polysorbates are prepared from sorbitol in a three-step process. Water is initially removed from the sorbitol to form a sorbitan (a cyclic sorbitol anhydride). The sorbitan is then partially esterified with a fatty acid, such as oleic or stearic acid, to yield a hexitan ester. Finally, ethylene oxide is chemically added in the presence of a catalyst to yield the polysorbate.

14 Safety

Polysorbates are widely used in cosmetics, food products, and oral, parenteral, and topical pharmaceutical formulations and are generally regarded as nontoxic and nonirritant materials. There have, however, been occasional reports of hypersensitivity to polysorbates following their topical and intramuscular use.(3) Polysorbates have also been associated with serious adverse effects, including some deaths, in low-birthweight infants intravenously administered a vitamin E preparation containing a mixture of polysorbates 20 and 80.(4,5) When heated to decomposition, the polysorbates emit acrid smoke and irritating fumes.

The WHO has set an estimated acceptable daily intake for polysorbates 20, 40, 60, 65, and 80, calculated as total polysorbate esters, at up to 25 mg/kg body-weight.(6)

Polysorbate 20: moderate toxicity by IP and IV routes. Moderately toxic by ingestion. Human skin irritant.
LD_{50} (hamster, oral): 18 g/kg(7)
LD_{50} (mouse, IV): 1.42 g/kg
LD_{50} (rat, oral): 37 g/kg
Polysorbate 21: moderately toxic by IV route.
Polysorbate 40: LD_{50} (rat, IV): 1.58 g/kg.(7) Moderately toxic by IV route.
Polysorbate 60: LD_{50} (rat, IV): 1.22 g/kg.(7) Moderately toxic by IV route. Experimental tumorigen; reproductive effects.
Polysorbate 61: moderately toxic by IV route.
Polysorbate 80: moderately toxic by IV route. Mildly toxic by ingestion. Eye irritation. Experimental tumorigen, reproductive effects. Mutogenic data.
LD_{50} (mouse, IP): 7.6 g/kg(7)
LD_{50} (mouse, IV): 4.5 g/kg
LD_{50} (mouse, oral): 25 g/kg
LD_{50} (rat, IP): 6.8 g/kg
LD_{50} (rat, IV): 1.8 g/kg
Polysorbate 85: skin irritant.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16 Regulatory Status

Polysorbates 60, 65, and 80 are GRAS listed. Polysorbates 20, 40, 60, 65, and 80 are accepted as food additives in Europe. Polysorbates 20, 40, 60, and 80 are included in the FDA Inactive Ingredients Guide (IM, IV, oral, rectal, topical, and vaginal preparations). Polysorbates are included in parenteral and nonparenteral medicines licensed in the UK. Polysorbates 20, 21, 40, 60, 61, 65, 80, 81, 85, and 120 are included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Polyethylene glycol; sorbitan esters (sorbitan fatty acid esters).

18 Comments

—

19 Specific References

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21 Authors

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22 Date of Revision

22 August 2005.

Polyoxyethylene Stearates

1 Nonproprietary Names

The polyoxyethylene stearates are a series of polyethoxylated derivatives of stearic acid. Of the large number of different materials commercially available, one type is listed in the USPNF 23.

JP: Polyoxyl 40 stearate
USPNF: Polyoxyl 40 stearate
See also Sections 2, 3, 4, and 5.

2 Synonyms

Ethoxylated fatty acid esters; macrogol stearates; *Marlosol*; PEG fatty acid esters; PEG stearates; polyethylene glycol stearates; poly(oxy-1,2-ethanediyl) α-hydro-ω-hydroxyoctadecanoate; polyoxyethylene glycol stearates.

Polyoxyethylene stearates are nonionic surfactants produced by polyethoxylation of stearic acid. Two systems of nomenclature are used for these materials. The number '8' in the names 'poloxyl 8 stearate' or 'polyoxyethylene 8 stearate' refers to the approximate polymer length in oxyethylene units. The same material may also be designated 'polyoxyethylene glycol 400 stearate' or 'macrogol stearate 400' in which case, the number '400' refers to the average molecular weight of the polymer chain.

For synonyms applicable to specific polyoxyethylene stearates, *see* Table I.

3 Chemical Name and CAS Registry Number

Polyethylene glycol stearate [9004-99-3]
Polyethylene glycol distearate [9005-08-7]

4 Empirical Formula and Molecular Weight

See Table II.

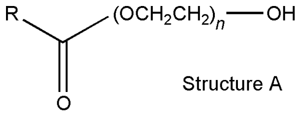
Table I: Synonyms of selected polyoxyethylene stearates and distearates.

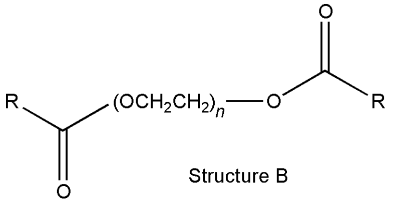
Name	Synonym
Polyoxyl 2 stearate	*Hodag DGS*; *Lipo DGS*; PEG-2 stearate.
Polyoxyl 4 stearate	*Acconon 200-MS*; *Hodag 20-S*; PEG-4 stearate; polyethylene glycol 200 monostearate; polyoxyethylene (4) monostearate; *Protamate 200-DPS*.
Polyoxyl 6 stearate	*Cerasynt 616*; *Kessco PEG 300 Monostearate*; *Lipal 300S*; *Lipo PEG 3-S*; PEG-6 stearate; polyethylene glycol 300 monostearate; polyoxyethylene (6) monostearate; *Polystate C*; *Protamate 300-DPS*.
Polyoxyl 8 stearate	*Acconon 400-MS*; *Cerasynt 660*; *Cithrol 4MS*; *Crodet S8*; *Emerest 2640*; *Grocor 400*; *Hodag 40-S*; *Kessco PEG-400 Monostearate*; *Lipo-PEG 4-S*; macrogol stearate 400; *Myrj 45*; PEG-8 stearate; *Pegosperse 400 MS*; polyethylene glycol 400 monostearate; polyoxyethylene (8) monostearate; *Protamate 400-DPS*; *Ritapeg 400 MS*.
Polyoxyl 12 stearate	*Hodag 60-S*; *Kessco PEG 600 Monostearate*; *Lipo-PEG 6-S*; PEG-12 stearate; *Pegosperse 600 MS*; polyethylene glycol 600 monostearate; polyoxyethylene (12) monostearate; *Protamate 600-DPS*.
Polyoxyl 20 stearate	*Cerasynt 840*; *Hodag 100-S*; *Kessco PEG 1000 Monostearate*; *Lipo-PEG 10-S*; *Myrj 49*; *Pegosperse 1000 MS*; PEG-20 stearate; polyethylene glycol 1000 monostearate; polyoxyethylene (20) monostearate; *Protamate 1000-DPS*.
Polyoxyl 30 stearate	*Myrj 51*; PEG-30 stearate; polyoxyethylene (30) stearate.
Polyoxyl 40 stearate	*Crodet S40*; E431; *Emerest 2672*; *Hodag POE (40) MS*; *Lipal 395*; *Lipo-PEG 39-S;* macrogol stearate 2000; *Myrj 52*; PEG-40 stearate; polyoxyethylene glycol 2000 monostearate; polyoxyethylene (40) monostearate; *Protamate 2000-DPS; Ritox 52*.
Polyoxyl 50 stearate	*Atlas G-2153*; *Crodet S50*; *Lipal 505*; *Myrj 53*; PEG-50 stearate; polyoxyethylene (50) monostearate.
Polyoxyl 100 stearate	*Lipo-PEG 100-S; Myrj 59*; PEG-100 stearate; polyethylene glycol 4400 monostearate; polyoxyethylene (100) monostearate; *Protamate 4400-DPS; Ritox 53*.
Polyoxyl 150 stearate	*Hodag 600-S*; PEG-150 stearate; *Ritox 59*.
Polyoxyl 4 distearate	*Hodag 22-S*; PEG-4 distearate.
Polyoxyl 8 distearate	*Hodag 42-S*; *Kessco PEG 400 DS*; PEG-8 distearate; polyethylene glycol 400 distearate; *Protamate 400-DS*.
Polyoxyl 12 distearate	*Hodag 62-S*; *Kessco PEG 600 Distearate*; PEG-12 distearate; polyethylene (12) distearate; polyethylene glycol 600 distearate; *Protamate 600-DS*.
Polyoxyl 32 distearate	*Hodag 154-S*; *Kessco PEG 1540 Distearate*; PEG-32 distearate; polyethylene glycol 1540 distearate; polyoxyethylene (32) distearate.
Polyoxyl 150 distearate	*Hodag 602-S*; *Kessco PEG 6000 DS*; *Lipo-PEG 6000-DS;* PEG-150 distearate; polyethylene glycol 6000 distearate; polyoxyethylene (150) distearate; *Protamate 6000-DS*.

Table II: Empirical formulas and molecular weights of selected polyoxyethylene stearates.

Name	Empirical formula	Molecular weight
Polyoxyl 6 stearate	$C_{30}H_{60}O_8$	548.80
Polyoxyl 8 stearate	$C_{34}H_{68}O_{10}$	636.91
Polyoxyl 12 stearate	$C_{42}H_{84}O_{14}$	813.12
Polyoxyl 20 stearate	$C_{58}H_{116}O_{22}$	1165.55
Polyoxyl 40 stearate	$C_{98}H_{196}O_{42}$	2046.61
Polyoxyl 50 stearate	$C_{118}H_{236}O_{52}$	2487.15
Polyoxyl 100 stearate	$C_{218}H_{436}O_{102}$	4689.80

5 Structural Formula





Structure A applies to the monostearate; where the average value of *n* is 6 for polyoxyl 6 stearate, 8 for polyoxyl 8 stearate, and so on.

Structure B applies to the distearate; where the average value of *n* is 12 for polyoxyl 12 distearate, 32 for polyoxyl 32 distearate, and so on.

In both structures, R represents the alkyl group of the parent fatty acid. With stearic acid, R is $CH_3(CH_2)_{16}$. However, it should be noted that stearic acid usually contains other fatty acids, primarily palmitic acid, and consequently a polyoxyethylene stearate may also contain varying amounts of other fatty acid derivatives such as palmitates.

6 Functional Category

Emulsifying agent; solubilizing agent; wetting agent.

7 Applications in Pharmaceutical Formulation or Technology

Polyoxyethylene stearates are generally used as emulsifiers in oil-in-water-type creams and lotions. Their hydrophilicity or lipophilicity depends on the number of ethylene oxide units present: the larger the number, the greater the hydrophilic properties. Polyoxyl 40 stearate has been used as an emulsifying agent in intravenous infusions.$^{(1)}$

Polyoxyethylene stearates are particularly useful as emulsifying agents when astringent salts or other strong electrolytes are present. They can also be blended with other surfactants to obtain any hydrophilic–lipophilic balance for lotions or ointment formulations. *See* Table III.

Table III: Uses of polyoxyethylene stearates.

Use	Concentration (%)
Auxiliary emulsifier for o/w intravenous fat emulsion	0.5–5
Emulsifier for o/w creams or lotions	0.5–10
Ophthalmic ointment	7
Suppository component	1–10
Tablet lubricant	1–2

8 Description

See Table IV.

Table IV: Description of various polyoxyethylene stearates.

Name	Description
Polyoxyl 6 stearate	Soft solid
Polyoxyl 8 stearate	Waxy cream
Polyoxyl 12 stearate	Pasty solid
Polyoxyl 20 stearate	Waxy solid
Polyoxyl 40 stearate	Waxy solid, with a faint, bland, fat-like odor, off-white to light tan in color
Polyoxyl 50 stearate	Solid, with a bland, fat-like odor or odorless
Polyoxyl 100 stearate	Solid
Polyoxyl 12 distearate	Paste
Polyoxyl 32 distearate	Solid
Polyoxyl 150 distearate	Solid

9 Pharmacopeial Specifications

See Table V.

Table V: Pharmacopeial specifications for polyoxyethylene stearates.

Test	JP 2001	USPNF 23
	Polyoxyl 40 stearate	**Polyoxyl 40 stearate**
Identification	+	+
Clarity and color of solution	+	—
Congealing range	39–44°C	37–47°C
Congealing point of the fatty acid	$\geqslant$53°C	—
Residue on ignition	$\leqslant$0.10%	—
Water	—	$\leqslant$3.0%
Arsenic	$\leqslant$3 ppm	—
Heavy metals	$\leqslant$10 ppm	$\leqslant$0.001%
Acid value	$\leqslant$1	$\leqslant$2
Hydroxyl value	—	25–40
Saponification value	25–35	25–35
Free polyethylene glycols	—	17–27%
Organic volatile impurities	—	+

10 Typical Properties

Flash point: >149°C for poloxyl 8 stearate (*Myrj 45*).

Solubility: *see* Table VI. *See also* Table VII.

Table VI: Solubility of polyoxyethylene stearates.

Name	Solvent		
	Ethanol (95%)	Mineral oil	Water
Polyoxyl 6 stearate	S	S	DH
Polyoxyl 8 stearate	S	I	D
Polyoxyl 12 stearate	S	I	S
Polyoxyl 20 stearate	S	I	S
Polyoxyl 40 stearate	S	I	S
Polyoxyl 50 stearate	S	I	S
Polyoxyl 100 stearate	S	I	S
Polyoxyl 12 distearate	S	—	DH
Polyoxyl 32 distearate	S	—	S
Polyoxyl 150 distearate	I	—	S

D = dispersible; I = insoluble; S = soluble; DH = dispersible (with heat).

11 Stability and Storage Conditions

Polyoxyethylene stearates are generally stable in the presence of electrolytes and weak acids or bases. Strong acids and bases can cause gradual hydrolysis and saponification.

The bulk material should be stored in a well-closed container, in a dry place, at room temperature.

12 Incompatibilities

Polyoxyethylene stearates are unstable in hot alkaline solutions owing to hydrolysis, and will also saponify with strong acids or bases. Discoloration or precipitation can occur with salicylates, phenolic substances, iodine salts, and salts of bismuth, silver, and tannins.(2–4) Complex formation with preservatives may also occur.(5) The antimicrobial activity of some materials such as bacitracin, chloramphenicol, phenoxymethylpenicillin, sodium penicillin, and tetracycline may be reduced in the presence of polyoxyethylene stearate concentrations greater than 5% w/w.(6,7)

13 Method of Manufacture

Polyoxyethylene stearates are prepared by the direct reaction of fatty acids, particularly stearic acid, with ethylene oxide.

14 Safety

Although polyoxyethylene stearates are primarily used as emulsifying agents in topical pharmaceutical formulations, certain materials, particularly polyoxyl 40 stearate, have also been used in intravenous injections and oral preparations.(1,4)

Polyoxyethylene stearates have been tested extensively for toxicity in animals(8–13) and are widely used in pharmaceutical formulations and cosmetics. They are generally regarded as essentially nontoxic and nonirritant materials.

Polyoxyl 8 stearate:
LD_{50} (hamster, oral): 27 g/kg
LD_{50} (rat, oral): 64 g/kg
Polyoxyl 20 stearate:
LD_{50} (mouse, IP): 0.2 g/kg
LD_{50} (mouse, IV): 0.87 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

Polyoxyethylene stearates that contain greater than 100 ppm of free ethylene oxide may present an explosion hazard when stored in a closed container. This is due to the release of ethylene oxide into the container headspace, where it can accumulate and so exceed the explosion limit.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (dental solutions; IV injections; ophthalmic preparations; oral capsules and tablets; otic suspensions; topical creams, emulsions, lotions, ointments, and solutions; and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Polyethylene glycol; stearic acid.

18 Comments

—

Table VII: Typical properties of polyoxyethylene stearates.

Name	Acid value	Free ethylene oxide	HLB value	Hydroxyl value	Iodine number	Melting point (°C)	Saponification value	Water content (%)
Polyoxyl 6 stearate	⩽5.0	⩽100 ppm	9.7	—	⩽0.5	28–32	95–110	—
Polyoxyl 8 stearate	⩽2.0	⩽100 ppm	11.1	87–105	⩽1.0	28–33	82–95	⩽3.0
Polyoxyl 12 stearate	⩽8.5	⩽100 ppm	13.6	55–75	⩽1.0	≈ 37	62–78	⩽1.0
Polyoxyl 20 stearate	⩽1.0	⩽100 ppm	14	50–62	⩽1.0	≈ 28	46–56	⩽1.0
Polyoxyl 30 stearate	⩽2.0	—	16	35–50	—	—	30–45	⩽3.0
Polyoxyl 40 stearate	⩽1.0	—	16.9	27–40	—	≈ 38	25–35	⩽3.0
Polyoxyl 50 stearate	⩽2.0	—	17.9	23–35	—	≈ 42	20–28	⩽3.0
Polyoxyl 100 stearate	⩽1.0	⩽100 ppm	18.8	15–30	—	≈ 46	9–20	⩽3.0
Polyoxyl 8 distearate	⩽10.0	—	—	⩽15	⩽0.5	≈ 36	115–124	—
Polyoxyl 12 distearate	⩽10.0	⩽100 ppm	10.6	⩽20	⩽1.0	≈ 39	93–102	⩽1.0
Polyoxyl 32 distearate	⩽10.0	⩽100 ppm	14.8	⩽20	⩽0.25	≈ 45	50–62	⩽1.0
Polyoxyl 150 distearate	7–9	⩽100 ppm	18.4	⩽15	⩽0.1	53–57	14–20	⩽1.0

19 Specific References

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21 Authors

SC Owen.

22 Date of Revision

31 August 2005.

Polyvinyl Acetate Phthalate

1 Nonproprietary Names

USPNF: Polyvinyl acetate phthalate

2 Synonyms

Phthalavin; PVAP; *Opaseal*; *Sureteric.*

3 Chemical Name and CAS Registry Number

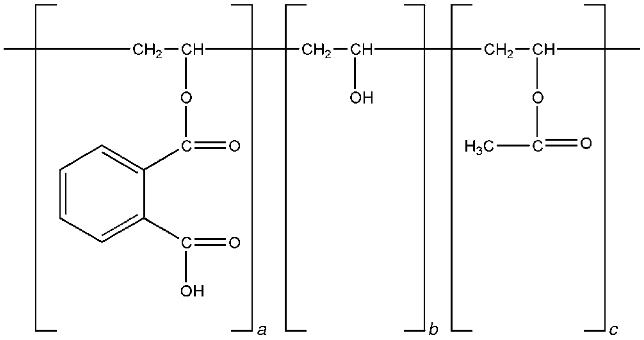
Polyvinyl acetate phthalate [34481-48-6]

4 Empirical Formula and Molecular Weight

The USPNF 23 describes polyvinyl acetate phthalate as a reaction product of phthalic anhydride and a partially hydrolyzed polyvinyl acetate. It contains not less than 55.0% and not more than 62.0% of phthalyl (*o*-carboxybenzoyl, $C_8H_5O_3$) groups, calculated on an anhydrous acid-free basis.

It has been reported that the free phthalic acid content is dependent on the source of the material.(1)

5 Structural Formula



Depending on the phthalyl content, *a* will vary with *b* in mole percent. The acetyl content *c* remains constant depending on the starting material.

6 Functional Category

Coating agent.

7 Applications in Pharmaceutical Formulation or Technology

Polyvinyl acetate phthalate is a viscosity-modifying agent that is used in pharmaceutical formulations to produce enteric coatings for products and for the core sealing of tablets prior to a sugar-coating process. Polyvinyl acetate phthalate does not exhibit tackiness during coating and produces strong robust films.

Plasticizers are often included in polyvinyl acetate phthalate coating formulations to enable a continuous, homogeneous, noncracking film to be produced. Polyvinyl acetate phthalate has been shown to be compatible with several plasticizers such as glyceryl triacetate, triethyl citrate, acetyl triethylcitrate, diethyl phthalate and polyethylene glycol 400.

For enteric coating applications, polyvinyl acetate phthalate is dissolved in a solvent system together with other additives such as diethyl phthalate and stearic acid. Methanol may be used as the solvent if a colorless film is required; for a colored film, methanol or ethanol/water may be used depending on the amount of pigment to be incorporated. A weight increase of up to 8% is necessary for nonpigmented systems, whereas for pigmented systems a weight increase of 6% is usually required. A formulated, aqueous-based coating solution (*Sureteric*, Colorcon) is available commercially for the enteric coating of tablets, hard and soft gelatin capsules and granules.

Polyvinyl acetate phthalate has superseded materials such as shellac in producing the initial layers of coating (the sealing coat) in the sugar coating process for tablets. The sealing coating should be kept as thin as possible while providing an adequate barrier to moisture, a balance that is often difficult to achieve in practice. A solvent system containing a high proportion of industrial methylated spirits and other additives can be used. Two coats are usually sufficient to seal most tablets, although up to five may be necessary for tablets containing alkaline ingredients. If an enteric coating is also required, between six and 12 coats may be necessary, *see* Table I.

The properties of polyvinyl acetate phthalate enteric coating have been compared with those of other enteric polymers such as cellulose acetate phthalate(2,3) and *Eudragit L 30D*.(3) The factors that affect the release kinetics from polyvinyl acetate phthalate enteric-coated tablets have also been described.(4) A method for enteric coating hypromellose capsules which avoids the sealing step prior to coating has been developed. The properties of several enteric coating polymers, including polyvinyl acetate phthalate, were assessed.(5)

Table I: Uses of polyvinyl acetate phthalate.

Use	Concentration (%)
Tablet enteric film coating	9–10
Tablet sealant (sugar-coating)	28–29

8 Description

Polyvinyl acetate phthalate is a free-flowing white to off-white powder and may have a slight odor of acetic acid. The material is essentially amorphous.(6)

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for polyvinyl acetate phthalate.

Test	USPNF 23
Identification	+
Apparent viscosity at 25°C	7–11 mPa s
Water	⩽5.0%
Residue on ignition	⩽1.0%
Free phthalic acid	⩽0.6%
Free acid other than phthalic	⩽0.6%
Organic volatile impurities	+
Phthalyl content	55.0–62.0%

10 Typical Properties

The characteristics of polyvinyl acetate phthalate from two sources have been compared; values for molecular weight (60 700; 47 000), moisture content (3.74%; 2.20%) and density ($1.31\,g/cm^3$; $1.37\,g/cm^3$) have been reported. The solubility of each polyvinyl acetate phthalate in a range of different solvents was described and scanning electron photomicrographs were produced to give evidence of the different polymer morphology.(7)

Glass transition temperature: a glass transition temperature of 42.5°C has been reported for polyvinyl acetate phthalate; the glass transition temperature was shown to fall with the addition of increasing amounts of the plasticizer diethyl phthalate.(6)

Solubility: soluble in ethanol and methanol; sparingly soluble in acetone and propan-2-ol; practically insoluble in chloroform, dichloromethane, and water. In buffer solutions, polyvinyl acetate phthalate (200 mg/L) is insoluble below pH 5 and becomes soluble at pH values above 5. Polyvinyl acetate pththalate shows a sharp solubility response with pH; this occurs at pH 4.5–5.0, which is lower than for most other polymers used for enteric coatings. Solubility is also influenced by ionic strength. *See* Table III.

Table III: Solubility of polyvinyl acetate phthalate.

Solvent	Solubility at 25°C
Acetone/ethanol (1 : 1 w/w)	1 in 3
Acetone/methanol (1 : 1 w/w)	1 in 4
Ethanol (95%)	1 in 4
Methanol	1 in 2
Methanol/dichloromethane (1 : 1 w/w)	1 in 3

Viscosity (dynamic): the viscosity of a solution of polyvinyl acetate phthalate:methanol (1 : 1) is 5000 mPa s. In methanol/dichloromethane systems, viscosity increases as the concentration of methanol in the system increases.

11 Stability and Storage Conditions

Polyvinyl acetate phthalate should be stored in airtight containers. It is relatively stable to temperature and humidity and does not age, giving predictable release profiles even after prolonged storage.

At high temperature and humidity, polyvinyl acetate phthalate undergoes less hydrolysis than other commonly used enteric coating polymers. In aqueous colloidal dispersions of polyvinyl acetate phthalate, the formation of free phthalic acid through hydrolysis was found to adversely affect physical stability.(1)

Following storage at room temperature for 9 months, capsules coated with a commercial polyvinyl acetate phthalate formulation (*Coateric*) were found to retain gastroresistant properties and showed no apparent physical change; however, a delayed drug dissolution profile was observed after storage. Storage at 37°C, or 37°C and 80% relative humidity, for 3 months resulted in capsules having an unsatisfactory appearance.(3)

12 Incompatibilities

Polyvinyl acetate phthalate reacts with povidone to form an insoluble complex that precipitates out of solution;(8) benzocaine is also incompatible with polyvinyl acetate phthalate.(9) Erythromycin disperses in polyvinyl acetate phthalate and has been shown to be physically stable(10) while omeprazole exists in the amorphous form in polyvinyl acetate phthalate coatings with no evidence of interaction.(11)

13 Method of Manufacture

Polyvinyl acetate phthalate is a reaction product of phthalic anhydride, sodium acetate, and a partially hydrolyzed polyvinyl alcohol. The polyvinyl alcohol is a low molecular weight grade, and 87–89 mole percent is hydrolyzed. Therefore, the polyvinyl acetate phthalate polymer is a partial esterification of a partially hydrolyzed polyvinyl acetate.

See also Section 4.

14 Safety

Polyvinyl acetate phthalate is used in oral pharmaceutical formulations and is generally regarded as an essentially nonirritant and nontoxic material when used as an excipient.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Gloves and eye protection are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (sustained-action oral tablet). Included in nonparenteral medicines licensed in Europe. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Cellulose acetate phthalate; hypromellose phthalate; polymethacrylates; shellac.

18 Comments

Polyvinyl acetate phthalate dissolves along the whole length of the duodenum.

19 Specific References

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20 General References

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21 Authors

CG Cable.

22 Date of Revision

23 August 2005.

Polyvinyl Alcohol

1 Nonproprietary Names

PhEur: Poly(vinylis acetas)
USP: Polyvinyl alcohol

2 Synonyms

Airvol; *Alcotex*; *Elvanol*; *Gelvatol*; *Gohsenol*; *Lemol*; *Mowiol*; *Polyvinol*; PVA; vinyl alcohol polymer.

3 Chemical Name and CAS Registry Number

Ethenol, homopolymer [9002-89-5]

4 Empirical Formula and Molecular Weight

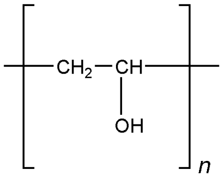
$(C_2H_4O)_n$ 20 000–200 000

Polyvinyl alcohol is a water-soluble synthetic polymer represented by the formula $(C_2H_4O)_n$. The value of n for commercially available materials lies between 500 and 5000, equivalent to a molecular weight range of approximately 20 000–200 000, *see* Table I.

Table I: Commercially available grades of polyvinyl acohol.

Grade	Molecular weight
High viscosity	~200 000
Medium viscosity	~130 000
Low viscosity	~20 000

5 Structural Formula



$$\left[-CH_2-\underset{\displaystyle OH}{\underset{|}{CH}}- \right]_n$$

6 Functional Category

Coating agent; lubricant; stabilizing agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Polyvinyl alcohol is used primarily in topical pharmaceutical and ophthalmic formulations; *see* Table II.(1–3) It is used as a stabilizing agent for emulsions (0.25–3.0% w/v). Polyvinyl alcohol is also used as a viscosity-increasing agent for viscous formulations such as ophthalmic products. It is used in artificial tears and contact lens solutions for lubrication purposes, in sustained-release formulations for oral administration,(4) and in transdermal patches.(5) Polyvinyl alcohol may be made into microspheres when mixed with a glutaraldehyde solution.(6)

Table II: Uses of polyvinyl alcohol.

Use	Concentration (%)
Emulsions	0.5
Ophthalmic formulations	0.25–3.00
Topical lotions	2.5

8 Description

Polyvinyl alcohol occurs as an odorless, white to cream-colored granular powder.

9 Pharmacopeial Specifications

See Table III.

Table III: Pharmacopeial specifications for polyvinyl alcohol.

Test	PhEur 2005	USP 28
Viscosity	—	+
pH	4.5–6.5	5.0–8.0
Loss on drying	⩽5.0%	⩽5.0%
Residue on ignition	⩽1.0%	⩽2.0%
Water-soluble substances	—	⩽0.1%
Degree of hydrolysis	—	⩽0.1%
Organic volatile impurities	—	+
Assay	—	85.0–115.0%

10 Typical Properties

Melting point:
228°C for fully hydrolyzed grades;
180–190°C for partially hydrolyzed grades.
Refractive index: $n_D^{25} = 1.49–1.53$
Solubility: soluble in water; slightly soluble in ethanol (95%); insoluble in organic solvents. Dissolution requires dispersion (wetting) of the solid in water at room temperature followed by heating the mixture to about 90°C for approximately 5 minutes. Mixing should be continued while the heated solution is cooled to room temperature.
Specific gravity:
1.19–1.31 for solid at 25°C;
1.02 for 10% w/v aqueous solution at 25°C.
Specific heat: 1.67 J/g (0.4 cal/g)
Viscosity (dynamic): *see* Table IV.

Table IV: Viscosity of commercial grades of polyvinyl alcohol.

Grade	Dynamic viscosity of 4% w/v aqueous solution at 20°C (mPa s)
High viscosity	40.0–65.0
Medium viscosity	21.0–33.0
Low viscosity	4.0–7.0

11 Stability and Storage Conditions

Polyvinyl alcohol is stable when stored in a tightly sealed container in a cool, dry place. Aqueous solutions are stable in corrosion-resistant sealed containers. Preservatives may be added to the solution if extended storage is required. Polyvinyl alcohol undergoes slow degradation at 100°C and rapid degradation at 200°C; it is stable on exposure to light.

12 Incompatibilities

Polyvinyl alcohol undergoes reactions typical of a compound with secondary hydroxy groups, such as esterification. It decomposes in strong acids, and softens or dissolves in weak acids and alkalis. It is incompatible at high concentration with inorganic salts, especially sulfates and phosphates; precipitation of polyvinyl alcohol 5% w/v can be caused by phosphates. Gelling of polyvinyl alcohol solution may occur if borax is present.

13 Method of Manufacture

Polyvinyl alcohol is produced through the hydrolysis of polyvinyl acetate. The repeating unit of vinyl alcohol is not used as the starting material because it cannot be obtained in the quantities and purity required for polymerization purposes. The hydrolysis proceeds rapidly in methanol, ethanol, or a mixture of alcohol and methyl acetate, using alkalis or mineral acids as catalysts.

14 Safety

Polyvinyl alcohol is generally considered a nontoxic material. It is nonirritant to the skin and eyes at concentrations up to 10%; concentrations up to 7% are used in cosmetics.

Studies in rats have shown that polyvinyl alcohol 5% w/v aqueous solution injected subcutaneously can cause anemia and infiltrate various organs and tissues.(7)

LD_{50} (mouse, oral): 14.7 g/kg
LD_{50} (rat, oral): >20 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Polyvinyl alcohol dust may be an irritant on inhalation. Handle in a well-ventilated environment.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (ophthalmic preparations and oral tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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18 Comments

Various grades of polyvinyl alcohol are commercially available. The degree of polymerization and the degree of hydrolysis are the two determinants of their physical properties. Pharmaceutical grades are partially hydrolyzed materials and are named according to a coding system. The first number following a trade name refers to the degree of hydrolysis and the second set of numbers indicates the approximate viscosity (dynamic), in mPa s, of a 4% w/v aqueous solution at 20°C.

19 Specific References

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21 Authors

O AbuBaker.

22 Date of Revision

12 August 2005.

Potassium Alginate

1 Nonproprietary Names

None adopted.

2 Synonyms

Alginic acid, potassium salt; E402; *Improved Kelmar*; potassium polymannuronate.

3 Chemical Name and CAS Registry Number

Potassium alginate [9005-36-1]

4 Empirical Formula and Molecular Weight

$(C_6H_7O_6K)_n$

Potassium alginate is the potassium salt of alginic acid, a polyuronide made up of a sequence of two hexuronic acid residues, namely D-mannuronic acid and L-guluronic acid. The two sugars form blocks of up to 20 units along the chain with the proportion of the blocks dependent on the species of seaweed and also the part of the seaweed used. The number and length of the blocks is important in determining the physical properties of the alginate produced; the number and sequence of the mannuronate and guluronate residues varies in the naturally occurring alginate.

5 Structural Formula

See Section 4.

6 Functional Category

Emulsifying agent; stabilizing agent; suspending agent; thickening agent.

7 Applications in Pharmaceutical Formulation or Technology

Potassium alginate is widely used in foods as a stabilizer, thickener, and emulsifier; however, its use as a pharmaceutical excipient is currently limited to experimental hydrogel systems. The viscosity, adhesiveness, elasticity, stiffness, and cohesiveness of potassium alginate hydrogels has been determined and compared with values from a range of other hydrogel-forming materials.(1) The effect of calcium ions on the rheological properties of procyanidin hydrogels containing potassium alginate and intended for oral administration has also been investigated.(2)

8 Description

Potassium alginate occurs as a white to yellowish, fibrous or granular powder; it is almost odorless and tasteless.

9 Pharmacopeial Specifications

See Section 18.

10 Typical Properties

Particle size distribution: average particle size ≈150 μm (*Improved Kelmar*)

Solubility: potassium alginate is soluble in water, dissolving to form a viscous hydrophilic colloidal solution. It is insoluble in ethanol (95%) and in hydroalcoholic solutions in which the alcohol content is greater than 30% by weight; also insoluble in chloroform, ether, and acids having a pH lower than about 3. When preparing solutions of potassium alginate it is important to ensure proper dispersion of the particles, as poor dispersion will lead to the formation of large lumps of unhydrated powder and significantly extended hydration times.

Viscosity (dynamic): 400 mPa s (for a 1% dispersion of *Improved Kelmar*). Vicosities of 4.32×10^3 mPa s (2.5% dispersion) and 31.1×10^3 mPa s (4% dispersion) have been reported.(1)

Potassium alginate hydrates readily in hot or cold water; in solution, the acid groups of the alginate become ionized and a viscous solution is obtained. The viscosity is proportional to the concentration and molecular weight of the material used. As the temperature rises, a reversible decrease in viscosity occurs. The addition of calcium ions to potassium alginate solutions results in crosslinking and in the formation of gels; where the crosslinks formed are strong and numerous, the gel becomes thermally irreversible.

11 Stability and Storage Conditions

In the solid state, potassium alginate is a stable material that is not prone to microbial spoilage. Over time, a slow reduction in the degree of polymerization can occur, which may be reflected in a reduction in the viscosity of solutions. As both temperature and moisture can impair the performance of potassium alginate, storage below 25°C is recommended.

Potassium alginate solutions are stable at pH 4–10; long-term storage outside this range can result in depolymerization of the polymer through hydrolysis. Gelation or precipitation of the alginate can occur at pH values less than 4. Liquid or semisolid alginate formulations should be preserved: suitable preservatives are sodium benzoate, potassium sorbate, or parabens.

Potassium alginate should be stored under cool, dry conditions in a well-closed container.

12 Incompatibilities

Incompatible with strong oxidizers.

13 Method of Manufacture

Alginate obtained from brown seaweed is subjected to demineralization, extraction, and precipitation of alginic acid. Following neutralization, the potassium alginate obtained is dried and milled.

14 Safety

Potassium alginate is widely used in food products. It is currently used as an excipient only in experimental pharmaceutical formulations.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. When heated to decomposition, potassium alginate emits acrid smoke and irritating fumes.

16 Regulatory Status

GRAS listed. Accepted for use in foods in the USA and Europe.

17 Related Substances

Alginic acid; ammonium alginate; calcium alginate; propylene glycol alginate; sodium alginate.

18 Comments

Although not included in any pharmacopeias, a specification for potassium alginate is contained in the Food Chemicals Codex (FCC); *see* Table I.

Table I: Food Chemicals Codex specifications for potassium alginate.[3]

Test	FCC 1996
Arsenic	⩽3 mg/kg
Heavy metals	⩽0.002% (as lead)
Lead	⩽5 mg/kg
Loss on drying	15.00%
Assay	89.2–105.5%

19 Specific References

1 Vennat B, Lardy F, Arvouey-Grand A, Pourrat A. Comparative texturometric analysis of hydrogels based on cellulose derivatives, carraghenates and alginates. Evaluation of adhesiveness. *Drug Dev Ind Pharm* 1998; **24**(1): 27–35.
2 Vennat B, Quan ZQ, Pouget MP, Pourrat A. Procyanidin hydrogels. Influence of calcium on the gelling of alginate solutions. *Drug Dev Ind Pharm* 2003; **20**(17): 2707–2714.
3 *Food Chemicals Codex*, 4th edn. Washington, DC: National Academy Press, 1996: 312

20 General References

—

21 Authors

CG Cable.

22 Date of Revision

22 August 2005.

Potassium Benzoate

1 Nonproprietary Names

USPNF: Potassium benzoate

2 Synonyms

Benzoate of potash; benzoic acid potassium salt; E212; kalium benzoat; potassium salt trihydrate; *ProBenz PG*.

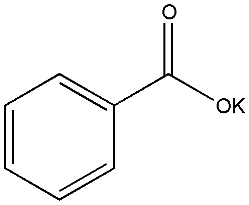
3 Chemical Name and CAS Registry Number

Potassium benzoate [582-25-2]

4 Empirical Formula and Molecular Weight

$C_7H_5KO_2$ 160.21

5 Structural Formula



6 Functional Category

Antimicrobial preservative; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Potassium benzoate is predominantly used as an antimicrobial preservative in a wide range of beverages, foods and some pharmaceutical formulations. Preservative efficacy increases with decreasing pH; it is most effective at pH 4.5 or below. However, at low pH undissociated benzoic acid may produce a slight though discernible taste in food products.

Increasingly, potassium benzoate is used as an alternative to sodium benzoate in applications where a low sodium content is desirable.

Therapeutically, potassium benzoate has also been used in the management of hypokalemia. *See also* Table I.

Table I: Uses of potassium benzoate.

Use	Concentration (%)
Carbonated beverages	0.03–0.08
Food products	⩽0.1

8 Description

Potassium benzoate occurs as a slightly hygroscopic, white, odorless or nearly odorless crystalline powder or granules. Aqueous solutions are slightly alkaline and have a sweetish astringent taste.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for potassium benzoate.

Test	USPNF 23
Identification	+
Alkalinity	+
Water	⩽1.5%
Heavy metals	⩽0.001%
Organic volatile impurities	+
Assay (anhydrous basis)	99.0–100.5%

10 Typical Properties

Acidity/alkalinity: aqueous solutions are slightly alkaline.
Melting point: >300°C
Solubility: *see* Table III.

Table III: Solubility of potassium benzoate.

Solvent	Solubility at 20°C unless otherwise stated
Ethanol (95%)	1 in 75
Ethanol (90%)	1 in 50
Ether	Practically insoluble
Methanol	Very slightly soluble
Water	1 in 2.46 at 13°C
	1 in 2.43 at 17.5°C
	1 in 2.36
	1 in 2.27 at 33.3°C
	1 in 2.23 at 41°C
	1 in 2.15 at 50°C

Specific gravity: 1.5

11 Stability and Storage Conditions

Potassium benzoate is stable at room temperature under normal storage conditions. Since it is slightly hygroscopic, potassium benzoate should be stored in sealed containers. Exposure to conditions of high humidity and elevated temperatures should be avoided.

12 Incompatibilities

Potassium benzoate is incompatible with strong acids and strong oxidizing agents.

13 Method of Manufacture

Potassium benzoate is prepared from the acid–base reaction between benzoic acid and potassium hydroxide.

14 Safety

Potassium benzoate is widely used in food products and is generally regarded as a nontoxic and nonirritant material. However, people with a history of allergies may show allergic reactions when exposed to potassium benzoate. Ingestion is inadvisable for asthmatics. Higher concentrations of potassium benzoate have been reported to cause irritation to mucous membranes.

The WHO acceptable daily intake of total benzoates including potassium benzoate, calculated as benzoic acid, has been estimated at up to 5 mg/kg of body-weight.(1,2)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Potassium benzoate may be irritant to the eyes and skin. Eye protection and gloves are recommended. When exposed to heat, and when heated to decomposition, potassium benzoate emits acrid smoke and irritating fumes.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Benzoic acid; sodium benzoate.

18 Comments

The EINECS number for potassium benzoate is 209-481-3.

19 Specific References

1 FAO/WHO. Toxicological evaluation of certain food additives with a review of general principles and of specifications. Seventeenth report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1974; No. 539.
2 FAO/WHO. Evaluation of certain food additives and contaminants. Twenty-seventh report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1983; No. 696.

20 General References

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21 Authors

CP McCoy.

22 Date of Revision

17 August 2005.

Potassium Bicarbonate

1 Nonproprietary Names

BP: Potassium bicarbonate
PhEur: Kalii hydrogenocarbonas
USP: Potassium bicarbonate

2 Synonyms

Carbonic acid monopotassium salt; E501; monopotassium carbonate; potassium acid carbonate; potassium hydrogen carbonate.

3 Chemical Name and CAS Registry Number

Potassium bicarbonate [298-14-6]

4 Empirical Formula and Molecular Weight

$KHCO_3$ 100.11

5 Structural Formula

$KHCO_3$

6 Functional Category

Alkalizing agent; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

As an excipient, potassium bicarbonate is generally used in formulations as a source of carbon dioxide in effervescent preparations, at concentrations of 25–50% w/w. It is of particular use in formulations where sodium bicarbonate is unsuitable, for example, when the presence of sodium ions in a formulation needs to be limited or is undesirable. Potassium bicarbonate is often formulated with citric acid or tartaric acid in effervescent tablets or granules; on contact with water, carbon dioxide is released through chemical reaction, and the product disintegrates. On occasion, the presence of potassium bicarbonate alone may be sufficient in tablet formulations, as reaction with gastric acid can be sufficient to cause effervescence and product disintegration.

Potassium bicarbonate has also been investigated as a gas-forming agent in alginate raft systems.(1,2)

Potassium bicarbonate is also used in food applications as an alkali and a leavening agent, and is a component of baking powder.

Therapeutically, potassium bicarbonate is used as an alternative to sodium bicarbonate in the treatment of certain types of metabolic acidosis. It is also used as an antacid to neutralize acid secretions in the gastrointestinal tract and as a potassium supplement.

8 Description

Potassium bicarbonate occurs as colorless, transparent crystals or as a white granular or crystalline powder. It is odorless, with a saline or weakly alkaline taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for potassium bicarbonate.

Test	PhEur 2005	USP 28
Identification	+	+
Characters	+	—
Appearance	+	—
Normal carbonates	—	≤2.5%
Chloride	≤150 ppm	—
Sulfate	≤150 ppm	—
Ammonium	≤20 ppm	—
Calcium	≤100 ppm	—
Heavy metals	≤10 ppm	≤0.001%
Iron	≤20 ppm	—
Sodium	≤0.5%	—
Loss on drying	—	≤0.3%
Organic volatile impurities	—	+
Assay	99.0–101.0%	99.5–101.5%

10 Typical Properties

Acidity/alkalinity: pH = 8.2 (for a 0.1 M aqueous solution)

Solubility: soluble 1 in 4.5 of water at 0°C, 1 in 2.8 of water at 20°C, 1 in 2 of water at 50°C; practically insoluble in ethanol (95%).

Specific gravity: 2.17

11 Stability and Storage Conditions

Potassium bicarbonate should be stored in a well-closed container in a cool, dry location. Potassium bicarbonate is stable in air at normal temperatures, but when heated to 100–200°C in the dry state, or in solution, it is gradually converted to potassium carbonate.

12 Incompatibilities

Potassium bicarbonate reacts with acids and acidic salts with the evolution of carbon dioxide.

13 Method of Manufacture

Potassium bicarbonate can be made by passing carbon dioxide into a concentrated solution of potassium carbonate, or by exposing moist potassium carbonate to carbon dioxide, preferably under moderate pressure.

Potassium bicarbonate also occurs naturally in the mineral calcinite.

14 Safety

Potassium bicarbonate is used in cosmetics, foods, and oral pharmaceutical formulations, where it is generally regarded as a relatively nontoxic and nonirritant material when used as an excipient. However, excessive consumption of potassium bicarbonate or other potassium salts may produce toxic manifestations of hyperkalemia.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe (the E number E501 refers to potassium carbonates). Included in nonparenteral medicines licensed in the UK and USA (chewable tablets; effervescent granules; effervescent tablets; lozenges; oral granules; oral suspensions). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Sodium bicarbonate.

18 Comments

One gram of potassium bicarbonate represents approximately 10 mmol of potassium and of bicarbonate; 2.56 g of potassium bicarbonate is approximately equivalent to 1 g of potassium. A specification for potassium bicarbonate is contained in the Food Chemicals Codex (FCC).

The EINECS number for potassium bicarbonate is 206-059-0.

19 Specific References

1 Johnson FA, Craig DQM, Mercer AD, Chauhan S. The effects of alginate molecular structure and formulation variables on the physical characteristics of alginate raft systems. *Int J Pharm* 1997; **159**: 35–42.

2 Johnson FA, Craig DQM, Mercer A, Chauhan S. The use of image analysis as a means of monitoring bubble formation in alginate rafts. *Int J Pharm* 1998; **170**: 179–185.

20 General References

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21 Authors

CG Cable.

22 Date of Revision

22 August 2005.

Potassium Chloride

1 Nonproprietary Names

BP: Potassium chloride
JP: Potassium chloride
PhEur: Kalii chloridum
USP: Potassium chloride

2 Synonyms

Chloride of potash; chloropotassuril; dipotassium dichloride; E508; potassium monochloride.

3 Chemical Name and CAS Registry Number

Potassium chloride [7447-40-7]

4 Empirical Formula and Molecular Weight

KCl 74.55

5 Structural Formula

KCl

6 Functional Category

Therapeutic agent; tonicity agent.

7 Applications in Pharmaceutical Formulation or Technology

Potassium chloride is widely used in a variety of parenteral and nonparenteral pharmaceutical formulations. Its primary use, in parenteral and ophthalmic preparations, is to produce isotonic solutions.

Potassium chloride is also used therapeutically in the treatment of hypokalemia.

Many solid-dosage forms of potassium chloride exist including: tablets prepared by direct compression(1–4) and granulation;(5,6) effervescent tablets; coated, sustained-release tablets;(7–10) sustained-release wax matrix tablets;(11) microcapsules;(12) pellets; and osmotic pump formulations.(13,14)

Experimentally, potassium chloride is frequently used as a model drug in the development of new solid-dosage forms, particularly for sustained-release or modified-release products.

Potassium chloride is also used widely in the food industry as a dietary supplement, pH control agent, stabilizer, thickener, and gelling agent. It can also be used in infant formulations.

8 Description

Potassium chloride occurs as odorless, colorless crystals or a white crystalline powder, with an unpleasant, saline taste. The crystal lattice is a face-centered cubic structure.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for potassium chloride.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Acidity or alkalinity	+	+	+
Appearance of solution	+	+	—
Loss on drying	⩽0.5%	⩽1.0%	⩽1.0%
Iodide or bromide	+	+	+
Aluminum	—	⩽1 ppm	⩽1 µg/g
Arsenic	⩽2 ppm	—	—
Barium	—	+	—
Calcium and magnesium	+	⩽200 ppm	+
Heavy metals	⩽5 ppm	⩽10 ppm	⩽0.001%
Iron	—	⩽20 ppm	—
Sodium	+	⩽0.1%	+
Sulfates	—	⩽300 ppm	—
Organic volatile impurities	—	—	+
Assay (dried basis)	⩾99.0%	99.0–100.5%	99.0–100.5%

10 Typical Properties

Acidity/alkalinity: pH ≈7 for a saturated aqueous solution at 15°C.
Boiling point: sublimes at 1500°C
Compressibility: *see* Figure 1.(3,4)
Density: 1.99 g/cm^3; 1.17 g/cm^3 for a saturated aqueous solution at 15°C.
Melting point: 790°C
Osmolarity: a 1.19% w/v solution is iso-osmotic with serum.
Particle size distribution: typical distribution(5) is 10% less than 30 µm, 50% less than 94 µm, and 90% less than 149 µm in size. Mean particle diameter is 108 µm. Finer powders may be obtained by milling.
Solubility: *see* Table II.

Table II: Solubility of potassium chloride.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	Practically insoluble
Ethanol (95%)	1 in 250
Ether	Practically insoluble
Glycerin	1 in 14
Water	1 in 2.8
	1 in 1.8 at 100°C

Specific surface area: 0.084 m^2/g (BET method)(5)

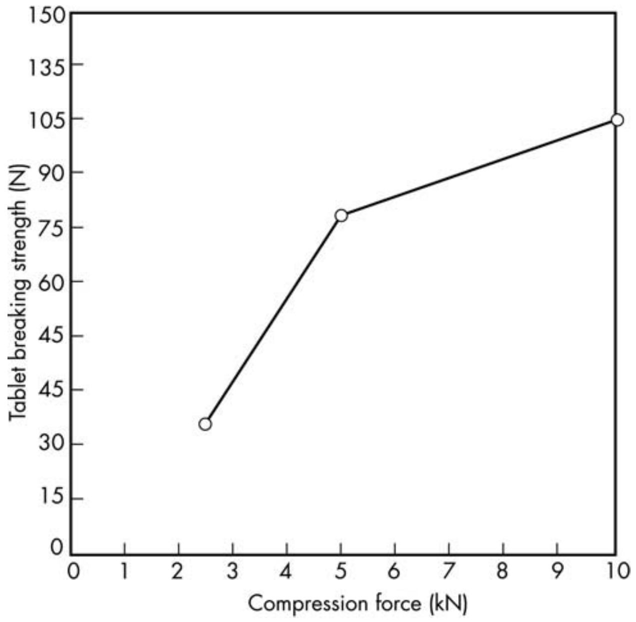

Figure 1: Compression characteristics of potassium chloride.[3] Tablet diameter = 10 mm.

11 Stability and Storage Conditions

Potassium chloride tablets become increasingly hard on storage at low humidities. However, tablets stored at 76% relative humidity showed no increase or only a slight increase in hardness.[2] The addition of lubricants, such as 2% w/w magnesium stearate,[1] reduces tablet hardness and hardness on aging.[2] Aqueous potassium chloride solutions may be sterilized by autoclaving or by filtration.

Potassium chloride is stable and should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Potassium chloride reacts violently with bromine trifluoride and with a mixture of sulfuric acid and potassium permanganate. The presence of hydrochloric acid, sodium chloride, and magnesium chloride decreases the solubility of potassium chloride in water. Aqueous solutions of potassium chloride form precipitates with lead and silver salts.

Intravenous aqueous potassium chloride solutions are incompatible with protein hydrolysate.

13 Method of Manufacture

Potassium chloride occurs naturally as the mineral sylvite or sylvine; it also occurs in other minerals such as sylvinite, carnallite, and kainite. Commercially, potassium chloride is obtained by the solar evaporation of brine or by the mining of mineral deposits.

14 Safety

Potassium chloride is used in a large number of pharmaceutical formulations including oral, parenteral, and topical preparations both as an excipient and as a therapeutic agent.

Potassium ions play an important role in cellular metabolism and imbalances can result in serious clinical effects. Orally ingested potassium chloride is rapidly absorbed from the gastrointestinal tract and excreted by the kidneys. Potassium chloride is more irritant than sodium chloride when adminstered orally, and ingestion of large quantities of potassium chloride can cause effects such as gastrointestinal irritation, nausea, vomiting, and diarrhea.

High localized concentrations of potassium chloride in the gastrointestinal tract can cause ulceration, hence the development of the many enteric-coated and wax matrix sustained-release preparations that are available.[15] Although it is claimed that some formulations cause less ulceration than others, it is often preferred to administer potassium chloride as an aqueous solution. However, solutions have also been associated with problems, mainly due to their unpleasant taste.

Parenterally, rapid injection of strong potassium chloride solutions can cause cardiac arrest; in the adult, solutions should be infused at a rate not greater than 750 mg/hour.

Therapeutically, in adults, up to 10 g orally, in divided doses has been administered daily, while intravenously up to 6 g daily has been used.

LD_{50} (guinea pig, oral): 2.5 g/kg[16]
LD_{50} (mouse, IP): 1.18 g/kg
LD_{50} (mouse, IV): 0.12 g/kg
LD_{50} (mouse, oral): 0.38 g/kg
LD_{50} (rat, IP): 0.66 g/kg
LD_{50} (rat, IV): 0.14 g/kg
LD_{50} (rat, oral): 2.6 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (injections, ophthalmic preparations, oral capsules, and tablets). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Sodium chloride.

18 Comments

Each gram of potassium chloride represents approximately 13.4 mmol of potassium; 1.91 g of potassium chloride is approximately equivalent to 1 g of potassium.

For diets where the intake of sodium chloride is restricted, salt substitutes for use in cooking or as table salt are available and contain mainly potassium chloride, e.g. *LoSalt* (Klinge Chemicals Ltd) is a blend of 2/3 potassium chloride and 1/3 sodium chloride with magnesium carbonate added as a flow-promoting agent. A specification for potassium chloride is contained in the Food Chemicals Codex (FCC).

The EINECS number for potassium chloride is 231-211-8.

19 Specific References

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14 Lindstedt B, Sjöberg M, Hjärtstam J. Osmotic pumping release from KCl tablets coated with porous and non-porous ethylcellulose. *Int J Pharm* 1991; **67**: 21–27.

15 McMahon FG, Ryan JR, Akdamar K, Ertan A. Effect of potassium chloride supplements on upper gastrointestinal mucosa. *Clin Pharmacol Ther* 1984; **35**: 852–855.

16 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 3025–3026.

20 General References

Love DW, Foster TS, Bradley DL. Comparison of the taste and acceptance of three potassium chloride preparations. *Am J Hosp Pharm* 1978; **35**(5): 586–588.

Staniforth JN, Rees JE. Segregation of vibrated powder mixes containing different concentrations of fine potassium chloride and tablet excipients. *J Pharm Pharmacol* 1983; **35**: 549–554.

21 Authors

SC Owen.

22 Date of Revision

9 August 2005.

Potassium Citrate

1 Nonproprietary Names

BP: Potassium citrate
PhEur: Kalii citras
USP: Potassium citrate

2 Synonyms

Citrate of potash; citric acid potassium salt; E332; tripotassium citrate monohydrate.

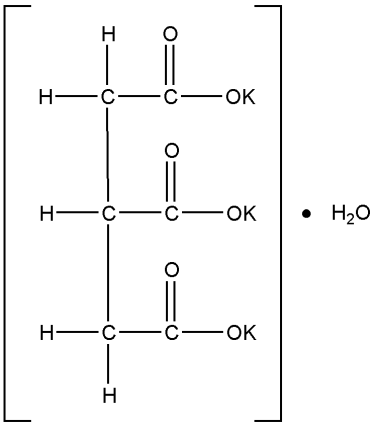
3 Chemical Name and CAS Registry Number

2-Hydroxy-1,2,3-propanetricarboxylic acid tripotassium salt monohydrate [6100-05-6]
2-Hydroxy-1,2,3-propanetricarboxylic acid tripotassium salt anhydrous [866-84-2]

4 Empirical Formula and Molecular Weight

$C_6H_5K_3O_7 \cdot H_2O$	324.41 (for monohydrate)
$C_6H_5K_3O_7$	306.40 (for anhydrous)

5 Structural Formula



6 Functional Category

Alkalizing agent; buffering agent; sequestering agent.

7 Applications in Pharmaceutical Formulation or Technology

Potassium citrate is used in beverages, foods, and oral pharmaceutical formulations as a buffering and alkalizing agent. It is also used as a sequestering agent and as a therapeutic agent to alkalinize the urine and to relieve the painful irritation caused by cystitis.(1–5) *See* Table I.

Table I: Uses of potassium citrate.

Use	Concentration (%)
Buffer for solutions	0.3–2.0
Sequestering agent	0.3–2.0

8 Description

Transparent prismatic crystals or a white, granular powder. Potassium citrate is hygroscopic and odorless, and has a cooling, saline taste.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for potassium citrate.

Test	PhEur 2005	USP 28
Identification	+	+
Characters	+	—
Acidity or alkalinity	+	+
Loss on drying	4.0–7.0%	3.0–6.0%
Appearance of solution	+	—
Tartrate	—	+
Heavy metals	⩽10 ppm	⩽0.001%
Sodium	⩽0.3%	—
Chlorides	⩽50 ppm	—
Oxalates	⩽300 ppm	—
Sulfates	⩽150 ppm	—
Organic volatile impurities	—	+
Readily carbonizable substances	+	—
Assay (dried basis)	99.0–101.0%	99.0–100.5%

10 Typical Properties

Acidity/alkalinity: pH = 8.5 (saturated aqueous solution).
Density: 1.98 g/cm^3
Melting point: 230°C (loses water of crystallization at 180°C).
Solubility: *see* Table III.

Table III: Solubility of potassium citrate.

Solvent	Solubility at 20°C
Ethanol (95%)	Practically insoluble
Glycerin	1 in 2.5
Water	1 in 0.65

11 Stability and Storage Conditions

Potassium citrate is a stable, though hygroscopic material, and should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Aqueous potassium citrate solutions are slightly alkaline and will react with acidic substances. Potassium citrate may also precipitate alkaloidal salts from their aqueous or alcoholic solutions. Calcium and strontium salts will cause precipitation of the corresponding citrates.

13 Method of Manufacture

Potassium citrate is prepared by adding either potassium bicarbonate or potassium carbonate to a solution of citric acid until effervescence ceases. The resulting solution is then filtered and evaporated to dryness to obtain potassium citrate.

14 Safety

Potassium citrate is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material by this route of administration.

Most potassium citrate safety data relate to its use as a therapeutic agent, for which up to 10 g may be administered daily, in divided doses, as a treatment for cystitis. Although there are adverse effects associated with excessive ingestion of potassium salts, the quantities of potassium citrate used as a pharmaceutical excipient are insignificant in comparison to those used therapeutically.

LD_{50} (IV, dog): 0.17 g/kg(6)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Potassium citrate may be irritant to the skin and eyes and should be handled in a well-ventilated environment. Eye protection and gloves are recommended. When heated to decomposition, potassium citrate emits toxic fumes of potassium oxide.(6)

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral solutions and suspensions; topical emulsions and aerosol foams). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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18 Comments

Each gram of potassium citrate monohydrate represents approximately 9.25 mmol of potassium and 3.08 mmol of citrate. Each gram of potassium citrate anhydrous represents approximately 9.79 mmol of potassium and 3.26 mmol of citrate. A specification for potassium citrate is contained in the Food Chemicals Codex (FCC). The EINECS number for potassium citrate is 212-755-5.

19 Specific References

1 Elizabeth JE, Carter NJ. Potassium citrate mixture: soothing but not harmless? *Br Med J* 1987; **295**: 993.
2 Gabriel R. Potassium sorbate mixture: soothing but not harmless? [letter] *Br Med J* 1987; **295**: 1487.
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4 Fjellstedt E, Denneberg T, Jeppsson JO, Tiselins HG. A comparison of the effects of potassium citrate and sodium bicarbonate in the alkalinization of urine in homozygous cystinuria. *Urol Res* 2001; **29**(5): 295–302.
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6 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 3026.

20 General References

Cole ET, Rees JE, Hersey JA. Relations between compaction data for some crystalline pharmaceutical materials. *Pharm Acta Helv* 1975; **50**: 28–32.

21 Authors

SC Owen.

22 Date of Revision

9 August 2005.

Potassium Hydroxide

1 Nonproprietary Names

BP: Potassium hydroxide
JP: Potassium hydroxide
PhEur: Kalii hydroxidum
USPNF: Potassium hydroxide

2 Synonyms

Caustic potash; E525; kalium hydroxydatum; potash lye; potassium hydrate.

3 Chemical Name and CAS Registry Number

Potassium hydroxide [1310-58-3]

4 Empirical Formula and Molecular Weight

KOH 56.11

5 Structural Formula

KOH

6 Functional Category

Alkalizing agent.

7 Applications in Pharmaceutical Formulation or Technology

Potassium hydroxide is widely used in pharmaceutical formulations to adjust the pH of solutions. It can also be used to react with weak acids to form salts.

Therapeutically, potassium hydroxide is used in various dermatological applications.

8 Description

Potassium hydroxide occurs as a white or nearly white fused mass. It is available in small pellets, flakes, sticks and other shapes or forms. It is hard and brittle and shows a crystalline fracture. Potassium hydroxide is hygroscopic and deliquescent; on exposure to air, it rapidly absorbs carbon dioxide and water with the formation of potassium carbonate.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for potassium hydroxide.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Appearance of solution	+	+	—
Aluminum	—	⩽0.2 ppm	—
Characters	—	+	—
Chloride	⩽0.05%	⩽50 ppm	—
Heavy metals	⩽30 ppm	⩽10 ppm	⩽0.003%
Insoluble substances	—	—	+
Iron	—	⩽10 ppm	—
Phosphates	—	⩽20 ppm	—
Potassium carbonate	⩽2.0%	⩽2.0%	—
Sodium	+	⩽1.0%	—
Sulfates	—	⩽50 ppm	—
Assay	⩾85.0%	85.0–100.5%	⩾85.0%

10 Typical Properties

Acidity/alkalinity: pH = 13.5 (0.1 M aqueous solution)
Melting point: 360°C; 380°C when anhydrous
Solubility: *see* Table II.

Table II: Solubility of potassium hydroxide.

Solvent	Solubility at 20°C unless otherwise stated
Ethanol (95%)	1 in 3
Ether	Practically insoluble
Glycerin	1 in 2.5
Water	1 in 0.9 1 in 0.6 at 100°C

11 Stability and Storage Conditions

Potassium hydroxide should be stored in an airtight, nonmetallic container in a cool, dry place.

12 Incompatibilities

Potassium hydroxide is a strong base and is incompatible with any compound that readily undergoes hydrolysis or oxidation. It should not be stored in glass or aluminum containers and will react with acids, esters, and ethers, especially in aqueous solution.

13 Method of Manufacture

Potassium hydroxide is made by the electrolysis of potassium chloride. Commercial grades may contain chlorides as well as other impurities.

14 Safety

Potassium hydroxide is widely used in the pharmaceutical and food industries and is generally regarded as a nontoxic material at low concentrations. At high concentrations it is a corrosive irritant to the skin, eyes, and mucous membranes.

LD_{50} (rat, oral): 0.273 g/kg(1)

15 Handling Precautions

Potassium hydroxide is a corrosive irritant to the skin, eyes, and mucous membranes. The solid and solutions cause burns, often with deep ulceration. It is very toxic on ingestion and harmful on inhalation. Observe normal handling precautions appropriate to the quantity and concentration of material handled. Gloves, eye protection, respirator, and other protective clothing should be worn.

Potassium hydroxide is strongly exothermic when dissolved in ethanol (95%) or water and considerable heat is generated. The reaction between potassium hydroxide solutions and acids is also strongly exothermic.

In the UK, the occupational exposure limit for potassium hydroxide has been set at 2 mg/m^3 short-term.(2)

16 Regulatory Status

GRAS listed. Accepted for use in Europe in certain food applications. Included in the FDA Inactive Ingredients Guide (injections, infusions, and oral capsules and solutions). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Sodium hydroxide.

18 Comments

A specification for potassium hydroxide is contained in the Food Chemicals Codex (FCC). The EINECS number for potassium hydroxide is 215-181-3.

19 Specific References

1 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 3033–3034.
2 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002.* Sudbury: HSE Books, 2002.

20 General References

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21 Authors

AH Kibbe.

22 Date of Revision

3 August 2005.

Potassium Metabisulfite

1 Nonproprietary Names

USPNF: Potassium metabisulfite

2 Synonyms

Disulfurous acid; dipotassium pyrosulfite; dipotassium salt; E224; kali disulfis; potassium pyrosulfite.

3 Chemical Name and CAS Registry Number

Dipotassium pyrosulfite [16731-55-8]

4 Empirical Formula and Molecular Weight

$K_2S_2O_5$ 222.32

5 Structural Formula

$K_2S_2O_5$

6 Functional Category

Antimicrobial preservative; antioxidant.

7 Applications in Pharmaceutical Formulation or Technology

Potassium metabisulfite is used in applications similar to those of sodium metabisulfite in pharmaceuticals and in the food, brewing, and wine making industries. It is used as an antioxidant, antimicrobial preservative and sterilizing agent.

8 Description

Potassium metabisulfite occurs as white or colorless free-flowing crystals, crystalline powder, or granules, usually with an odor of sulfur dioxide.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for potassium metabisulfite.

Test	USPNF 23
Identification	+
Iron	⩽0.001%
Heavy metals	⩽0.001%
Organic volatile impurities	+
Assay (as SO_2)	51.8–57.6%

10 Typical Properties

Acidity/alkalinity: 3.5–4.5 (5% w/v aqueous solution)
Density (bulk): 1.1–1.3 g/cm^3
Density (tapped): 1.2–1.5 g/cm^3
Melting point: 190°C although potassium metabisulfite decomposes at temperatures above 150°C.
Solubility: soluble 1 in 2.2 of water; practically insoluble in ethanol (95%).

11 Stability and Storage Conditions

Potassium metabisulfite should be stored in a cool, dark place. When stored at a maximum temperature of 25°C and maximum relative humidity of 45%, the shelf-life is 6 months. Potassium metabisulfite decomposes at temperatures above 150°C. In the air, it oxidizes to the sulfate, more readily in the presence of moisture.

In aqueous solution, potassium metabisulfite forms potassium bisulfite ($KHSO_3$) which exerts a strong reducing effect.

12 Incompatibilities

Potassium metabisulfite is incompatible with strong acids, water, and most common metals. It reacts with nitrites and sodium nitrate at room temperature, which occasionally results in the formation of flame. The reaction may be explosive if water is present. Potassium metabisulfite liberates SO_2 with acids.

Sulfites, including potassium metabisulfite, can react with various pharmaceutical compounds including sympathomimetics such as epinephrine (adrenaline),(1) chloramphenicol,(1) cisplatin,(2) and amino acids(3), which can result in their pharmacological inactivation. Sulfites are also reported to react with phenylmercuric nitrate,(4,5) and may adsorb onto rubber closures.

See also Section 18.

13 Method of Manufacture

—

14 Safety

Potassium metabisulfite is used in a variety of foods and pharmaceutical preparations, including oral, otic, rectal, and parenteral preparations. Potassium metabisulfite is considered a very irritating material, and may cause dermatitis on exposed skin.(6,7)

Hypersensitivity reactions to potassium metabisulfite and other sulfites, mainly used as preservatives in food products, have been reported. Reactions include bronchospasm and anaphylaxis; some deaths have also been reported, especially in those with a history of asthma or atopic allergy.(8–11) These reactions have led to restrictions by the FDA on the use of sulfites in food applications.(12) However, this restriction has not been extended to their use in pharmaceutical applications. Indeed, epinephrine (adrenaline) injections used to treat severe allergic reactions may contain sulfites.(11,12)

The WHO has set an acceptable daily intake of sulfites, as SO_2, at up to 0.35 mg/kg body-weight.(13)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Protective gloves and safety goggles are recommended, and precautions should be taken to minimize exposure to the mucous membranes and respiratory tract. When heated to decomposition, it emits toxic fumes of SO_2. *See also* Section 12.

16 Regulatory Status

GRAS listed. Accepted in Europe for use as a food additive in certain applications. Included in the FDA Inactive Ingredients Guide (IM and IV injections, otic and rectal solutions and suspensions). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Potassium bisulfite; sodium metabisulfite.

Potassium bisulfite

Empirical formula: $KHSO_3$
Molecular weight: 120.2
CAS number: [7773-03-7]
Synonyms: E228; potassium acid sulfite; potassium bisulphite; potassium hydrogen sulfite.
Comments: accepted in Europe as a food additive in certain applications. Included in food and pharmaceutical applications similarly to potassium metabisulfite.

18 Comments

Like all sulfites, potassium metabisulfite is not recommended for use in foods that are a source of thiamin, owing to the instability of the vitamin in their presence. Such foods include meat, raw fruits and vegetables, fresh potatoes, and foods that are a source of vitamin B_{12}. A specification for potassium metabisulfite is contained in the Food Chemicals Codex (FCC).

The EINECS number for potassium metabisulfite is 240-795-3.

19 Specific References

1 Higuchi T, Schroeter LC. Reactivity of bisulfite with a number of pharmaceuticals. *J Am Pharm Assoc (Sci)* 1959; **48**: 535–540.
2 Garren KW, Repta AJ. Incompatibility of cisplatin and Reglan Injectable. *Int J Pharm* 1985; **24**: 91–99.
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8 Mathison DA, Stevenson DD, Simon RA. Precipitating factors in asthma: aspirin, sulfites, and other drugs and chemicals. *Chest* 1985; **87** (Suppl.): 50S–54S.
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12 Anonymous. Warning for prescription drugs containing sulfites. *FDA Drug Bull* 1987; **17**: 2–3.
13 FAO/WHO. Evaluation of the toxicity of a number of antimicrobials and antioxidants. Sixth report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1962; No. 228.

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21 Authors

PJ Sheskey.

22 Date of Revision

23 August 2005.

Potassium Sorbate

1 Nonproprietary Names

BP: Potassium sorbate
PhEur: Kalii sorbas
USPNF: Potassium sorbate

2 Synonyms

E202; 2,4-hexadienoic acid (*E*,*E*)-potassium salt; potassium (*E*,*E*)-hexa-2,4-dienoate; potassium (*E*,*E*)-sorbate; sorbic acid potassium salt.

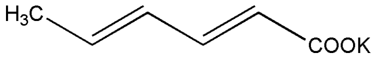
3 Chemical Name and CAS Registry Number

2,4-Hexadienoic acid potassium salt [24634-61-5]

4 Empirical Formula and Molecular Weight

$C_6H_7O_2K$ 150.22

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

Potassium sorbate is an antimicrobial preservative, with antibacterial and antifungal properties used in pharmaceuticals, foods, enteral preparations, and cosmetics. Generally, it is used at concentrations of 0.1–0.2% in oral and topical formulations, especially those containing nonionic surfactants. Potassium sorbate has been used to enhance the ocular bioavailability of timolol.(1)

Potassium sorbate is used in approximately twice as many pharmaceutical formulations as is sorbic acid owing to its greater solubility and stability in water. Like sorbic acid, potassium sorbate has minimal antibacterial properties in formulations above pH 6.

8 Description

Potassium sorbate occurs as a white crystalline powder with a faint, characteristic odor.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for potassium sorbate.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Acidity or alkalinity	+	+
Loss on drying	⩽1.0%	⩽1.0%
Heavy metals	⩽10 ppm	⩽0.001%
Organic volatile impurities	—	+
Aldehydes (as C_2H_4O)	⩽0.15%	—
Assay (dried basis)	99.0–101.0%	98.0–101.0%

10 Typical Properties

Antimicrobial activity: potassium sorbate is predominantly used as an antifungal preservative although it also has antibacterial properties. Similarly to sorbic acid, the antimicrobial activity is dependent on the degree of dissociation; there is practically no antibacterial activity above pH 6. Preservative efficacy is increased with increasing temperature,(2) and increasing concentration of potassium sorbate.(2) The efficacy of potassium sorbate is also increased when used in combination with other antimicrobial preservatives or glycols since synergistic effects occur.(3) Reported minimum inhibitory concentrations (MICs) at the pH values indicated are shown in Table II.(3)

Table II: Minimum inhibitory concentrations (MIC) of potassium sorbate.

Microorganism	MIC (μg/mL) at the stated pH		
	5.5	6.0	7.0
Escherichia coli	1400	1500	3800
Pseudomonas aeruginosa	1600–2300	1900–2500	5600–9000
Staphylococcus aureus	1200	1000	3800

Density: 1.363 g/cm^3
Melting point: 270°C with decomposition.
Solubility: *see* Table III.

11 Stability and Storage Conditions

Potassium sorbate is more stable in aqueous solution than sorbic acid; aqueous solutions may be sterilized by autoclaving.

The bulk material should be stored in a well-closed container, protected from light, at a temperature not exceeding 40°C.

12 Incompatibilities

Some loss of antimicrobial activity occurs in the presence of nonionic surfactants and some plastics. *See also* Sorbic Acid.

Table III: Solubility of potassium sorbate.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	1 in 1000
Benzene	Practically insoluble
Chloroform	Very slightly soluble
Corn oil	Very slightly soluble
Ethanol	1 in 50
Ethanol (95%)	1 in 35
Ethanol (5%)	1 in 1.7
Ether	Very slightly soluble
Propylene glycol	1 in 1.8
	1 in 2.1 at 50°C
	1 in 5 at 100°C
Water	1 in 1.72
	1 in 1.64 at 50°C
	1 in 1.56 at 100°C

13 Method of Manufacture

Potassium sorbate is prepared from sorbic acid and potassium hydroxide.

14 Safety

Potassium sorbate is used as an antimicrobial preservative in oral and topical pharmaceutical formulations and is generally regarded as a relatively nontoxic material. However, some adverse reactions to potassium sorbate have been reported, including irritant skin reactions which may be of the allergic, hypersensitive type. There have been no reports of adverse systemic reactions following oral consumption of potassium sorbate.

The WHO has set an estimated total acceptable daily intake for sorbic acid, calcium sorbate, potassium sorbate, and sodium sorbate expressed as sorbic acid at up to 25 mg/kg body-weight.(4,5)

LD_{50} (mouse, IP): 1.3 g/kg(6)
LD_{50} (rat, oral): 4.92 g/kg
See also Sorbic Acid.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Potassium sorbate is irritant to the skin, eyes, and mucous membranes; eye, protection and gloves are recommended. In areas of limited ventilation, a respirator is also recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (nasal sprays; oral capsules, solutions, suspensions, syrups, tablets; topical creams and lotions). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Sorbic acid.

18 Comments

Much of the information contained in the sorbic acid monograph on safety, incompatibilities, and references also applies to potassium, calcium, and sodium sorbates. *See* Sorbic Acid for further information.

Potassium sorbate has less antimicrobial activity than sorbic acid, but is more water soluble. Most potassium sorbate compounds will contain sorbic acid. A specification for potassium sorbate is contained in the Food Chemicals Codex (FCC).

The EINECS number for potassium sorbate is 246-376-1.

19 Specific References

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21 Authors

SC Owen.

22 Date of Revision

9 August 2005.

Povidone

1 Nonproprietary Names

BP: Povidone
JP: Povidone
PhEur: Povidonum
USP: Povidone

2 Synonyms

E1201; *Kollidon*; *Plasdone*; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.

3 Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4 Empirical Formula and Molecular Weight

$(C_6H_9NO)_n$ 2500–3 000 000

The USP 28 describes povidone as a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the differing degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a *K*-value, in the range 10–120. The *K*-value is calculated using Fikentscher's equation:(1)

$$\log z = c\left[\frac{75k^2}{1 + 1.5kc}\right] + k$$

where z is the relative viscosity of the solution of concentration c (in % w/v), and k is the *K*-value × 10^{-3}.

Alternatively, the *K*-value may be determined from the following equation:

$$K\text{-value} = \sqrt{\frac{300c \log z\,(c + 1.5c \log z)^2 + 1.5}{0.15c + 0.003c^2}}$$

where z is the relative viscosity of the solution of concentration c (in % w/v).

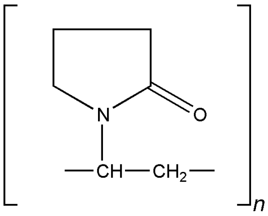
Approximate molecular weights for different povidone grades are shown in Table I.

Table I: Approximate molecular weights for different grades of povidone.

K-value	Approximate molecular weight
12	2 500
15	8 000
17	10 000
25	30 000
30	50 000
60	400 000
90	1 000 000
120	3 000 000

See also Section 8.

5 Structural Formula



6 Functional Category

Disintegrant; dissolution aid; suspending agent; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes.(2,3) Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.(4–6) Povidone solutions may also be used as coating agents.

Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone. *See* Table II.

Special grades of pyrogen-free povidone are available and have been used in parenteral formulations; *see* Section 14.

Table II: Uses of povidone.

Use	Concentration (%)
Carrier for drugs	10–25
Dispersing agent	Up to 5
Eye drops	2–10
Suspending agent	Up to 5
Tablet binder, tablet diluent, or coating agent	0.5–5

8 Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with *K*-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher *K*-value povidones are manufactured by drum drying and occur as plates.

9 Pharmacopeial Specifications

See Table III.

Table III: Pharmacopeial specifications for povidone.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	—	+	—
pH	—	+	3.0–7.0
$K \leqslant 30$	3.0–5.0	3.0–5.0	—
$K > 30$	4.0–7.0	4.0–7.0	—
Appearance of solution	+	+	—
Viscosity	—	+	—
Water	⩽5.0%	⩽5.0%	⩽5.0%
Residue on ignition	⩽0.1%	⩽0.1%	⩽0.1%
Lead	—	—	⩽10 ppm
Aldehydes	⩽500 ppm[a]	⩽500 ppm[a]	⩽0.05%
Hydrazine	⩽1 ppm	⩽1 ppm	⩽1 ppm
Vinylpyrrolidinone	⩽10 ppm	⩽10 ppm	⩽0.2%
Peroxides	⩽400 ppm[b]	⩽400 ppm[b]	—
K-value	25–90	—	10–120
⩽15	90.0–108.0%	85.0–115.0%	85.0–115.0%
>15	90.0–108.0%	90.0–108.0%	90.0–108.0%
Heavy metals	⩽10 ppm	⩽10 ppm	—
Assay (nitrogen content)	11.5–12.8%	11.5–12.8%	11.5–12.8%

[a] Expressed as acetaldehyde.
[b] Expressed as hydrogen peroxide.

10 Typical Properties

Acidity/alkalinity: pH = 3.0–7.0 (5% w/v aqueous solution).
Density (bulk): 0.29–0.39 g/cm^3 for *Plasdone*.
Density (tapped): 0.39–0.54 g/cm^3 for *Plasdone*.
Density (true): 1.180 g/cm^3
Flowability:
20 g/s for povidone K-15;
16 g/s for povidone K-29/32.
Melting point: softens at 150°C.
Moisture content: povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities. *See* Figures 1 and 2.

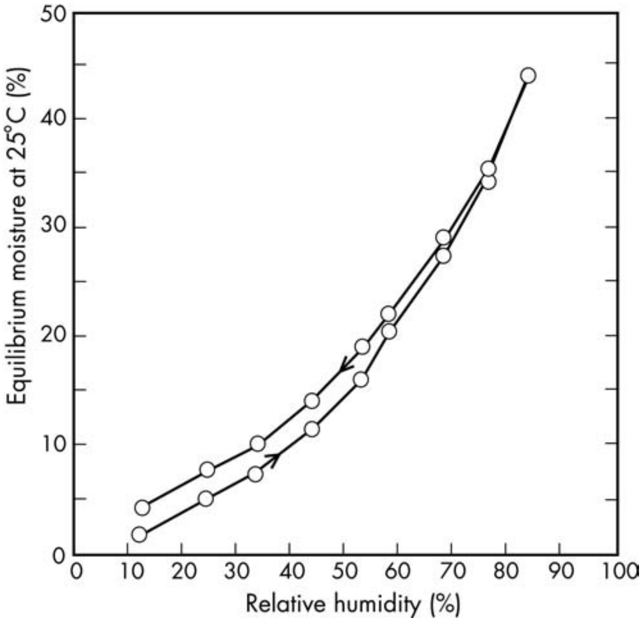


Figure 1: Sorption–desorption isotherm of povidone K-15 (*Plasdone K-15*).

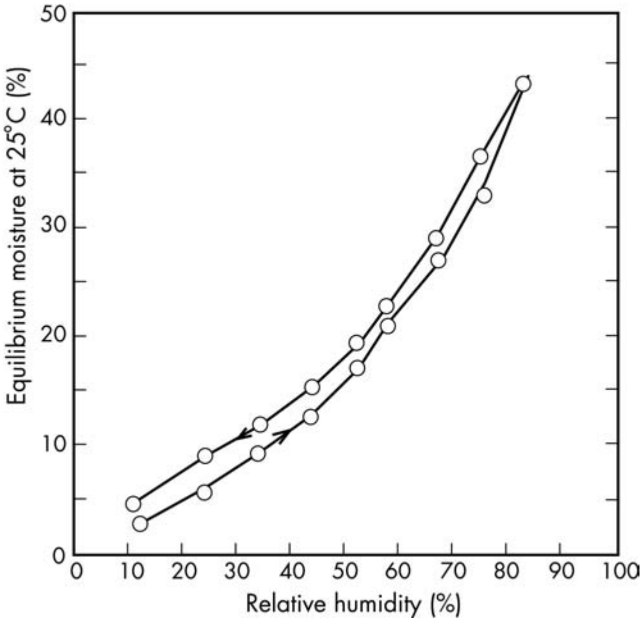


Figure 2: Sorption–desorption isotherm of povidone K-29/32 (*Plasdone K-29/32*).

Particle size distribution:
Kollidon 25/30: 90% >50 μm, 50% >100 μm, 5% >200 μm;
Kollidon 90: 90% >200 μm, 95% >250 μm.(7)
Solubility: freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the *K*-value.
Viscosity (dynamic): the viscosity of aqueous povidone solutions depends on both the concentration and the molecular weight of the polymer employed. *See* Tables IV and V.(7)

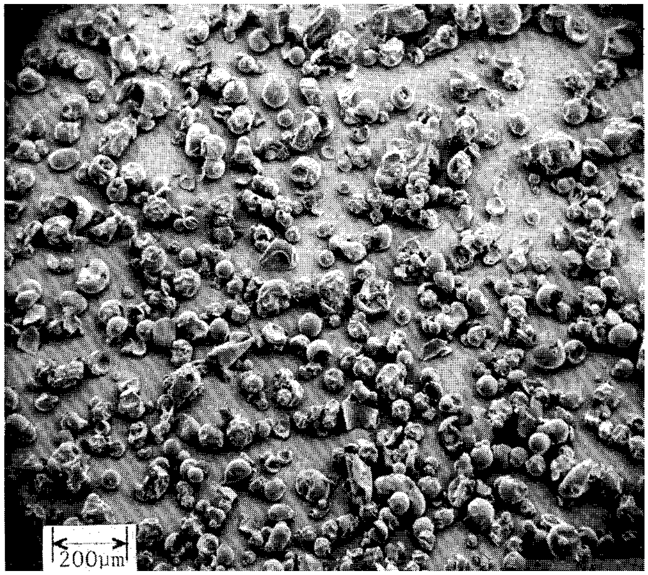
Table IV: Dynamic viscosity of 10% w/v aqueous povidone (*Kollidon*) solutions at 20°C.(7)

Grade	Dynamic viscosity (mPa s)
K-11/14	1.3–2.3
K-16/18	1.5–3.5
K-24/27	3.5–5.5
K-28/32	5.5–8.5
K-85/95	300–700

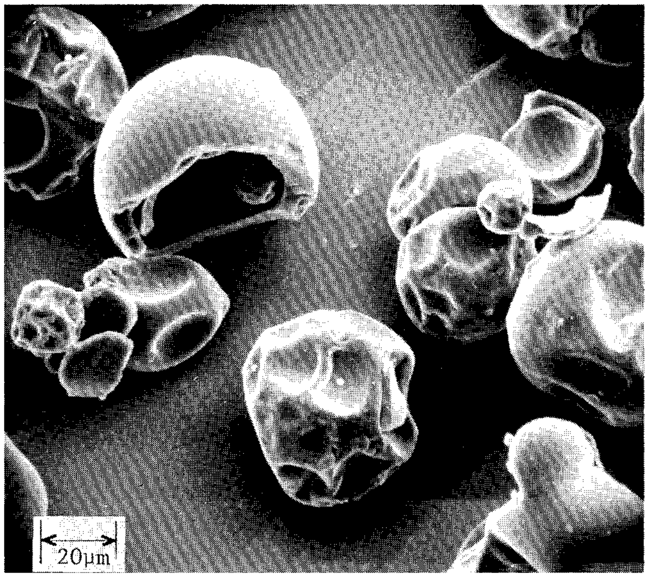
Table V: Dynamic viscosity of 5% w/v povidone (*Kollidon*) solutions in ethanol (95%) and propan-2-ol at 25°C.(7)

Grade	Dynamic viscosity (mPa s)	
	Ethanol (95%)	Propan-2-ol
K-12PF	1.4	2.7
K-17PF	1.9	3.1
K-25	2.7	4.7
K-30	3.4	5.8
K-90	53.0	90.0

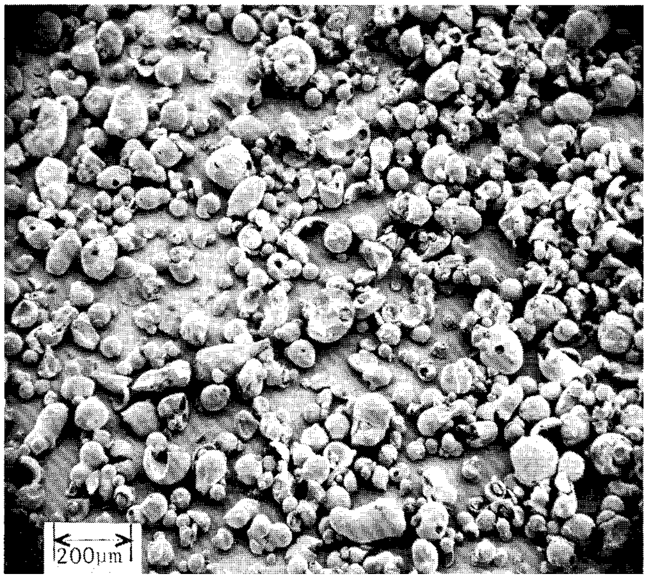
SEM: 1
Excipient: Povidone K-15 (*Plasdone K-15*)
Manufacturer: ISP
Lot No.: 82A-1
Magnification: 60×
Voltage: 5 kV



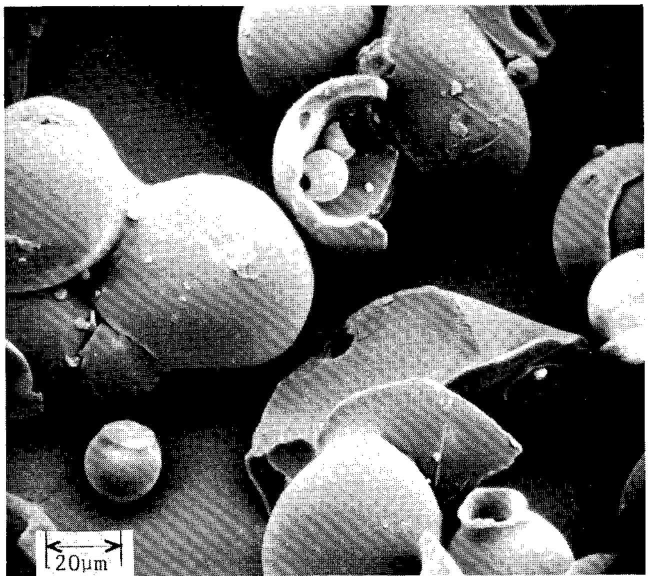
SEM: 2
Excipient: Povidone K-15 (*Plasdone K-15*)
Manufacturer: ISP
Lot No.: 82A-1
Magnification: 600×
Voltage: 5 kV



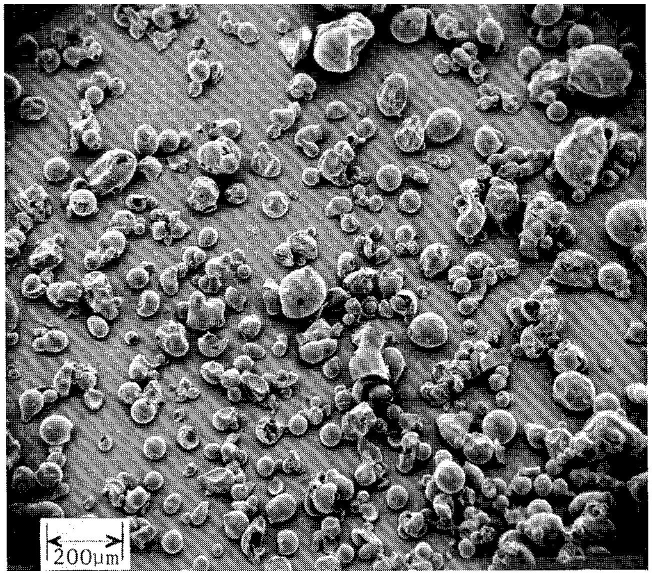
SEM: 3
Excipient: Povidone K-26/28 (*Plasdone K-26/28*)
Manufacturer: ISP
Lot No.: 82A-2
Magnification: 60×
Voltage: 5 kV



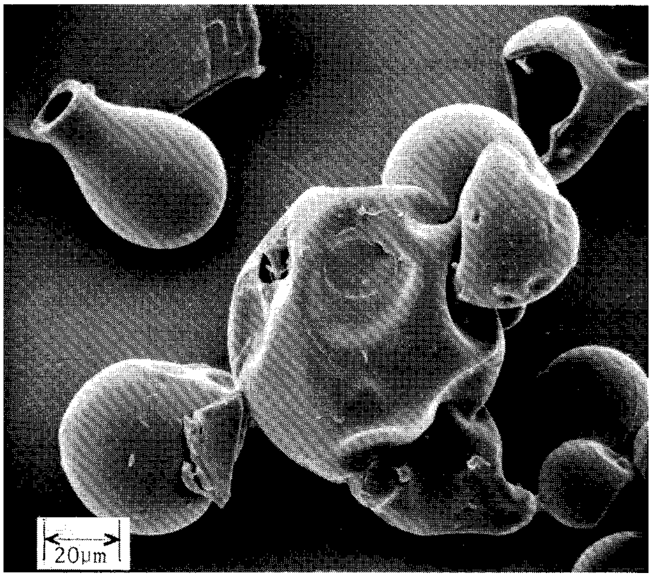
SEM: 4
Excipient: Povidone K-26/28 (*Plasdone K-26/28*)
Manufacturer: ISP
Lot No.: 82A-2
Magnification: 600×
Voltage: 10 kV



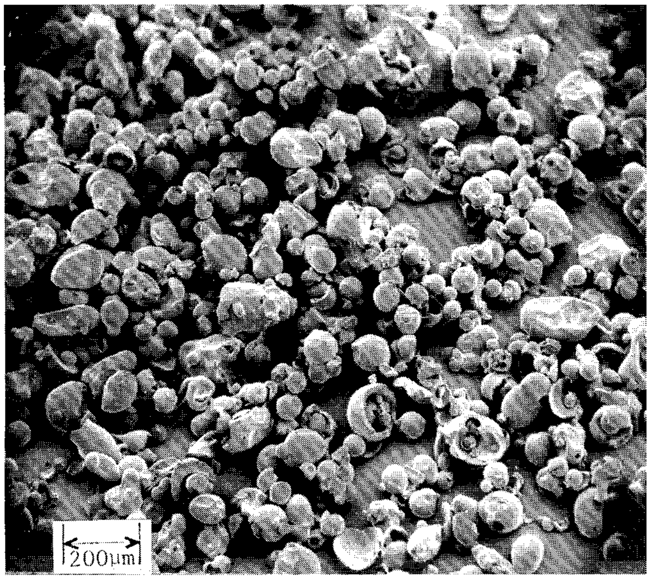
SEM: 5
Excipient: Povidone K-30 (*Plasdone K-30*)
Manufacturer: ISP
Lot No.: 82A-4
Magnification: 60×
Voltage: 10 kV



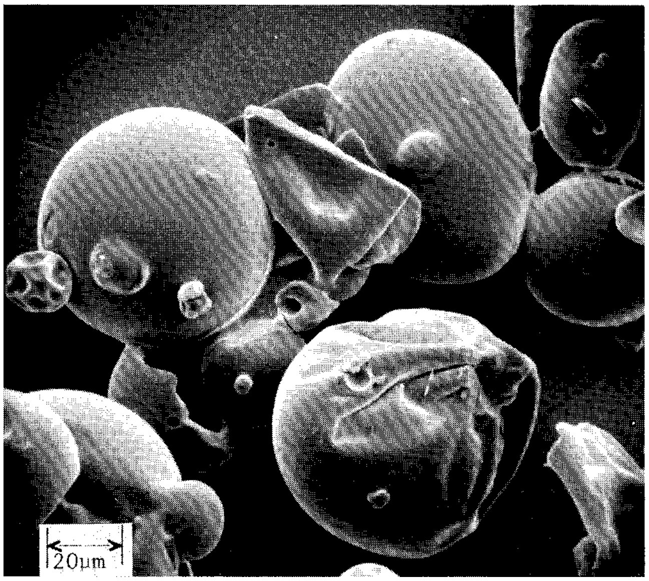
SEM: 6
Excipient: Povidone K-30 (*Plasdone K-30*)
Manufacturer: ISP
Lot No.: 82A-4
Magnification: 600×
Voltage: 10 kV



SEM: 7
Excipient: Povidone K-29/32 (*Plasdone K-29/32*)
Manufacturer: ISP
Lot No.: 82A-3
Magnification: 60×
Voltage: 5 kV



SEM: 8
Excipient: Povidone K-29/32 (*Plasdone K-29/32*)
Manufacturer: ISP
Lot No.: 82A-3
Magnification: 600×
Voltage: 10 kV



11 Stability and Storage Conditions

Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130°C; steam sterilization of an aqueous solution does not alter its properties. Aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives.

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds; *see* Section 18. The efficacy of some preservatives, e.g. thimerosal, may be adversely affected by the formation of complexes with povidone.

13 Method of Manufacture

Povidone is manufactured by the Reppe process. Acetylene and formaldehyde are reacted in the presence of a highly active copper acetylide catalyst to form butynediol, which is hydrogenated to butanediol and then cyclodehydrogenated to form butyrolactone. Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reaction in which pyrrolidone and acetylene are reacted under pressure. The monomer, vinylpyrrolidone, is then polymerized in the presence of a combination of catalysts to produce povidone.

14 Safety

Povidone has been used in pharmaceutical formulations for many years, being first used in the 1940s as a plasma expander, although it has now been superseded for this purpose by dextran.(8)

Povidone is widely used as an excipient, particularly in oral tablets and solutions. When consumed orally, povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes.(8) Povidone additionally has no irritant effect on the skin and causes no sensitization.

Reports of adverse reactions to povidone primarily concern the formation of subcutaneous granulomas at the injection site of intramuscular injections formulated with povidone.(9) Evidence also exists that povidone may accumulate in the organs of the body following intramuscular injection.(10)

A temporary acceptable daily intake for povidone has been set by the WHO at up to 25 mg/kg body-weight.(11)

LD_{50} (mouse, IP): 12 g/kg(12)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

16 Regulatory Status

Accepted for use in Europe as a food additive. Included in the FDA Inactive Ingredients Guide (IM and IV injections; ophthalmic preparations; oral capsules, drops, granules, suspensions, and tablets; sublingual tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Crospovidone.

18 Comments

The molecular adduct formation properties of povidone may be used advantageously in solutions, slow-release solid-dosage forms, and parenteral formulations. Perhaps the best-known example of povidone complex formation is povidone–iodine, which is used as a topical disinfectant.

For accurate standardization of solutions, the water content of the solid povidone must be determined before use and taken into account for any calculations. A specification for povidone is contained in the Food Chemicals Codex (FCC).

19 Specific References

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3 Stubberud L, Arwidsson HG, Hjortsberg V, Graffner C. Water–solid interactions. Part 3. Effect of glass transition temperature, T_g and processing on tensile strength of compacts of lactose and lactose/polyvinyl pyrrolidone. *Pharm Dev Technol* 1996; **1**(2): 195–204.

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7 BASF Corporation. Technical literature: *Soluble Kollidon Grades, Soluble Polyvinylpyrrolidone for the Pharmaceutical Industry*, 1997.

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21 Authors

AH Kibbe.

22 Date of Revision

30 August 2005.

Propionic Acid

1 Nonproprietary Names

USPNF: Propionic acid

2 Synonyms

Carboxyethane; ethanecarboxylic acid; E280; ethylformic acid; metacetonic acid; methylacetic acid; propanoic acid; pseudoacetic acid.

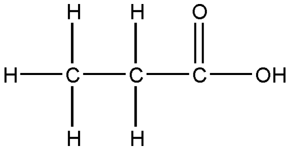
3 Chemical Name and CAS Registry Number

Propionic acid [79-09-4]

4 Empirical Formula and Molecular Weight

$C_3H_6O_2$ 74.08

5 Structural Formula



$H{-}\overset{H}{\underset{H}{C}}{-}\overset{H}{\underset{H}{C}}{-}\overset{O}{\overset{\|}{C}}{-}OH$

6 Functional Category

Acidifying agent; antimicrobial preservative; antioxidant; esterifying agent.

7 Applications in Pharmaceutical Formulation or Technology

Propionic acid is primarily used as an antioxidant and antimicrobial preservative in foods, and in oral and topical pharmaceutical applications. It is also used as an esterifying agent.

8 Description

Propionic acid occurs as a corrosive, oily liquid having a slightly pungent, disagreeable, rancid odor. It is flammable.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for propionic acid.

Test	USPNF 23
Specific gravity	0.988–0.993
Distilling range	138.5–142.5°C
Heavy metals	$\leqslant$0.001%
Limit of nonvolatile residue	$\leqslant$0.01%
Readily oxidizable substances	+
Limit of aldehydes	+
Organic volatile impurities	+
Assay	99.5–100.5%

10 Typical Properties

Antimicrobial activity: *see* Table II.

Table II: Typical minimum inhibitory concentrations (MICs) for propionic acid at pH 3.9.[1]

Microorganism	MIC (μg/mL)
Aspergillus niger	2000
Candida albicans	2000
Escherichia coli	2000
Klebsiella pneumoniae	1250
Penicillium notatum	2000
Pseudomonas aeruginosa	3000
Pseudomonas cepacia	3000
Pseudomonas fluorescens	1250
Staphylococcus aureus	2000

Autoignition temperature: 955°C
Boiling point: 141.1°C
Dissociation constant: $pK_a = 4.874$
Flash point: 52–58°C (open cup)
Melting point: −21.5°C
Partition coefficients: Octanol : water = 0.33.
Refractive index: $n_D^{25} = 1.3848$
Solubility: miscible with chloroform, ethanol (95%), ether, and water.
Specific gravity: 0.9934
Surface tension: 27.21 mN/m (27.21 dynes/cm) at 15°C
Vapor density (relative): 2.56 (air = 1)
Vapor pressure: 320 Pa (2.4 mmHg) at 20°C
Viscosity (dynamic): *see* Table III.

Table III: Dynamic viscosity of propionic acid.

Viscosity (dynamic)/mPa s	Temperature
1.175	15°C
1.02	25°C
0.956	30°C
0.668	60°C
0.495	90°C

11 Stability and Storage Conditions

Although stable, propionic acid is flammable. It should be stored in an airtight container away from heat and flames.

12 Incompatibilities

Propionic acid is incompatible with alkalis, ammonia, amines, and halogens. It can be salted out of aqueous solutions by the addition of calcium chloride or other salts.

13 Method of Manufacture

Propionic acid can be obtained from wood pulp waste liquor by fermentation. It can also be prepared from ethylene, carbon monoxide and steam; from ethanol and carbon monoxide using boron trifluoride catalyst; from natural gas; or as a by-product in the pyrolysis of wood. Very pure propionic acid can be obtained from propionitrile. Propionic acid can be found in dairy products in small amounts.

14 Safety

Propionic acid is generally regarded as a nontoxic and nonirritant material when used as an excipient. Up to 1% may be used in food applications (up to 0.3% in flour and cheese products). *See also* Sodium Propionate.

LD_{50} (mouse, IV): 0.63 g/kg(2)
LD_{50} (rabbit, skin): 0.5 g/kg
LD_{50} (rat, oral): 2.6 g/kg

15 Handling Precautions

Propionic acid is corrosive and can cause eye and skin burns. It may be harmful if swallowed, inhaled or absorbed through the skin as a result of prolonged or widespread contact. Eye protection, PVC gloves, and suitable protective clothing should be worn. Propionic acid should be handled in a well-ventilated environment away from heat and flames. In the UK, the occupational exposure limits for propionic acid are 31 mg/m^3 (10 ppm) long-term (8-hour TWA) and 46 mg/m^3 (15 ppm) short-term.(3)

16 Regulatory Status

GRAS listed. Accepted for use in Europe as a food additive. In Japan, propionic acid is restricted to use as a flavoring agent.

17 Related Substances

Sodium propionate.

18 Comments

A specification for propionic acid is contained in the Food Chemicals Codex (FCC). The EINECS number for propionic acid is 201-176-3.

19 Specific References

1 Wallhäusser KH. Propionic acid. In: Kabara JJ, ed. *Cosmetic and Drug Preservation: Principles and Practice*. New York: Marcel Dekker, 1984: 665–666.
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3 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.

20 General References

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21 Authors

GE Amidon.

22 Date of Revision

24 August 2005.

Propyl Gallate

1 Nonproprietary Names

BP: Propyl gallate
PhEur: Propylis gallas
USPNF: Propyl gallate

2 Synonyms

E310; gallic acid propyl ester; *n*-propyl gallate; *Progallin P*; propyl 3,4,5-trihydroxybenzoate; *Tenox PG*.

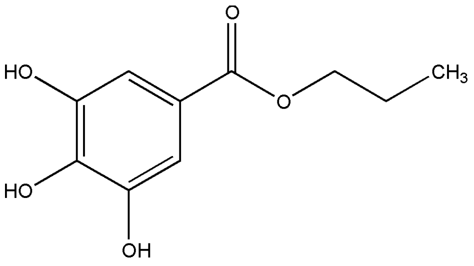
3 Chemical Name and CAS Registry Number

3,4,5-Trihydroxybenzoic acid propyl ester [121-79-9]

4 Empirical Formula and Molecular Weight

$C_{10}H_{12}O_5$ 212.20

5 Structural Formula



6 Functional Category

Antioxidant.

7 Applications in Pharmaceutical Formulation or Technology

Propyl gallate has become widely used as an antioxidant in cosmetics, perfumes, foods, and pharmaceuticals since its use in preventing autoxidation of oils was first described in 1943.(1,2) It is primarily used, in concentrations up to 0.1% w/v, to prevent the rancidity of oils and fats;(3) it may also be used at concentrations of 0.002% w/v to prevent peroxide formation in ether, and at 0.01% w/v to prevent the oxidation of paraldehyde. Synergistic effects with other antioxidants such as butylated hydroxyanisole and butylated hydroxytoluene have been reported. Propyl gallate is also said to possess some antimicrobial properties; *see* Section 10.

Studies have shown that, when added to powder blends containing ketorolac, propyl gallate significantly increases the drug stability in the preparation.(4)

Other alkyl gallates are also used as antioxidants and have approximately equivalent antioxidant properties when used in equimolar concentration; however, solubilities vary, *see* Section 17.

8 Description

Propyl gallate is a white, odorless or almost odorless crystalline powder, with a bitter astringent taste that is not normally noticeable at the concentrations employed as an antioxidant.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for propyl gallate.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Melting range	—	146–150°C
Appearance of solution	+	—
Gallic acid	+	—
Loss on drying	⩽0.5%	⩽0.5%
Residue on ignition	—	⩽0.1%
Sulfated ash	⩽0.1%	⩽0.1%
Total chlorine	⩽200 ppm	—
Chloride	⩽100 ppm	—
Heavy metals	⩽10 ppm	⩽0.001%
Zinc	⩽25 ppm	—
Organic volatile impurities	—	+
Assay (dried basis)	97.0–103.0%	98.0–102.0%

10 Typical Properties

Acidity/alkalinity: pH = 5.9 (0.1% w/v aqueous solution)

Antimicrobial activity: propyl gallate has been reported to possess some antimicrobial activity against Gram-negative, Gram-positive, and fungal species.(5) Its effectiveness as a preservative may be improved when used in combination with zinc salts, such as zinc sulfate, owing to synergistic effects.(6) For reported minimum inhibitory concentrations (MICs) for aqueous solutions containing 4% v/v ethanol as cosolvent, *see* Table II.(5)

Table II: Minimum inhibitory concentrations (MICs) for aqueous solutions containing propyl gallate and 4% v/v ethanol.

Microorganism	MIC (mg/mL)
Candida albicans	1500
Escherichia coli	330
Staphylococcus aureus	600

Dissociation constant: $pK_a = 8.11$

Melting point: 150°C

Partition coefficients:

Octanol : water = 32;
Oleyl alcohol : water = 17.

Solubility: *see* Table III.

Table III: Solubility of propyl gallate.

Solvent	Solubility at 20°C unless otherwise stated
Almond oil	1 in 44
Castor oil	1 in 4.5
Cottonseed oil	1 in 81 at 30°C
Ethanol (95%)	1 in 3 1 in 0.98 at 25°C
Ether	1 in 3 1 in 1.2 at 25°C
Lanolin	1 in 16.7 at 25°C
Lard	1 in 88 at 45°C
Mineral oil	1 in 200
Peanut oil	1 in 2000
Propylene glycol	1 in 2.5 at 25°C
Soybean oil	1 in 100 at 25°C
Water	1 in 1000 1 in 286 at 25°C

11 Stability and Storage Conditions

Propyl gallate is unstable at high temperatures and is rapidly destroyed in oils that are used for frying purposes.

The bulk material should be stored in a well-closed, nonmetallic container, protected from light, in a cool, dry place.

12 Incompatibilities

The alkyl gallates are incompatible with metals, e.g. sodium, potassium, and iron, forming intensely colored complexes. Complex formation may be prevented, under some circumstances, by the addition of a sequestering agent, typically citric acid. Propyl gallate may also react with oxidizing materials.

13 Method of Manufacture

Propyl gallate is prepared by the esterification of 3,4,5-trihydroxybenzoic acid (gallic acid) with *n*-propanol. Other alkyl gallates are prepared similarly using an appropriate alcohol of the desired alkyl chain length.

14 Safety

It has been reported, following animal studies, that propyl gallate has a strong contact sensitization potential.(7) Propyl gallate has also produced cytogenic effects in CHO-K1 cells.(8) However, despite this, there have been few reports of adverse reactions to propyl gallate.(9) Those that have been described include contact dermatitis; allergic contact dermatitis;(9–11) and methemoglobinemia in neonates.(12)

The WHO has set an estimated acceptable daily intake for propyl gallate at up to 1.4 mg/kg body-weight.(13)

LD_{50} (cat, oral): 0.4 g/kg(14)
LD_{50} (mouse, oral): 1.7 g/kg
LD_{50} (rat, oral): 2.1 g/kg
LD_{50} (rat, IP): 0.38 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. When heated to decomposition, propyl gallate may emit toxic fumes and smoke.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IM injections, oral, and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Dodecyl gallate; ethyl gallate; octyl gallate.

Dodecyl gallate

Empirical formula: $C_{19}H_{30}O_5$
Molecular weight: 338.44
CAS number: [1166-52-5]
Synonyms: dodecyl 3,4,5-trihydroxybenzoate; dodecylis gallas; E312; lauryl gallate.
Appearance: white, odorless or almost odorless, crystalline powder.
Melting point: 96–97.5°C
Solubility: *see* Table IV.

Table IV: Solubility of dodecyl gallate.

Solvent	Solubility at 20°C
Acetone	1 in 2
Chloroform	1 in 60
Ethanol (95%)	1 in 3.5
Ether	1 in 4
Methanol	1 in 1.5
Peanut oil	1 in 30
Propylene glycol	1 in 60
Water	Practically insoluble

Safety: the WHO has established a temporary estimated acceptable daily intake for dodecyl gallate at up to 0.05 mg/kg body-weight.(13)
Comments: the EINECS number for dodecyl gallate is 214-620-6.

Ethyl gallate

Empirical formula: $C_9H_{10}O_5$
Molecular weight: 198.17
CAS number: [831-61-8]
Synonyms: ethyl 3,4,5-trihydroxybenzoate.
Appearance: white, odorless or almost odorless, crystalline powder.
Melting point: 151–154°C
Solubility: *see* Table V.

Table V: Solubility of ethyl gallate.

Solvent	Solubility at 20°C
Ethanol (95%)	1 in 3
Ether	1 in 3
Peanut oil	Practically insoluble
Water	Slightly soluble

Octyl gallate

Empirical formula: $C_{15}H_{22}O_5$
Molecular weight: 282.34
CAS number: [1034-01-1]

Synonyms: E311; octyl 3,4,5-trihydroxybenzoate.
Appearance: white, odorless or almost odorless, crystalline powder.
Melting point: 100–102°C
Solubility: *see* Table VI.

Table VI: Solubility of octyl gallate.

Solvent	Solubility at 20°C
Acetone	1 in 1
Chloroform	1 in 30
Ethanol (95%)	1 in 2.5
Ether	1 in 3
Methanol	1 in 0.7
Peanut oil	1 in 33
Propylene glycol	1 in 7
Water	Practically insoluble

Safety: the WHO has established a temporary estimated acceptable daily intake for octyl gallate at up to 0.1 mg/kg body-weight.(13)
Comments: the EINECS number for octyl gallate is 252-073-5.

18 Comments

Propyl gallate has been reported to impart an 'off' flavor to corn and cottonseed oils when used as an antioxidant.(15) A specification for propyl gallate is contained in the Food Chemicals Codex (FCC). The EINECS number for propyl gallate is 204-498-2.

19 Specific References

1 Boehm E, Williams R. The action of propyl gallate on the autoxidation of oils. *Pharm J* 1943; **151**: 53.
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5 Zeelie JJ, McCarthy TJ. The potential antimicrobial properties of antioxidants in pharmaceutical systems. *S Afr Pharm J* 1982; **49**: 552–554.
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8 Tayama S, Nakagawa Y. Cytogenetic effects of propyl gallate in CHO-K1 cells. *Mutat Res* 2001; **498**(1–2): 117–127.
9 Golightly LK, Smolinske SS, Bennett ML, Sutherland EW, Rumack BH. Pharmaceutical excipients: adverse effects associated with 'inactive' ingredients in drug products (part II). *Med Toxicol* 1988; **3**: 209–240.
10 Cusano F, Capozzi M, Errico G. Safety of propyl gallate in topical products. *J Am Acad Dermatol* 1987; **17**: 308–309.
11 Bojs G, Nicklasson B, Svensson A. Allergic contact dermatitis to propyl gallate. *Contact Dermatitis* 1987; **17**: 294–298.
12 Nitzan M, Volovitz B, Topper E. Infantile methemoglobinemia caused by food additives. *Clin Toxicol* 1979; **15**(3): 273–280.
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14 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 3084.
15 McConnell JEW, Esselen WB. Effect of storage conditions and antioxidants on the keeping quality of packaged oils. *J Am Oil Chem Soc* 1947; **24**: 6–14.

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Johnson DM, Gu LC. Autoxidation and antioxidants. In: Swarbrick J, Boylan JC, eds. *Encyclopedia of Pharmaceutical Technology*, volume **1**. New York: Marcel Dekker, 1988: 415–449.

21 Authors

PJ Weller.

22 Date of Revision

9 August 2005.

Propylene Carbonate

1 Nonproprietary Names

USPNF: Propylene carbonate

2 Synonyms

Carbonic acid, cyclic propylene ester; cyclic methylethylene carbonate; cyclic propylene carbonate; 4-methyl-2-oxo-1,3-dioxolane; 1,2-propanediol cyclic carbonate; 1,2-propylene carbonate.

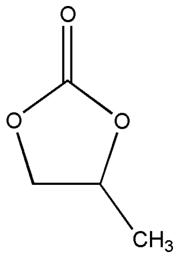
3 Chemical Name and CAS Registry Number

±-4-Methyl-1,3-dioxolan-2-one [108-32-7]

4 Empirical Formula and Molecular Weight

$C_4H_6O_3$ 102.09

5 Structural Formula



6 Functional Category

Gelling agent; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Propylene carbonate is used mainly as a solvent in oral and topical pharmaceutical formulations.

In topical applications, propylene carbonate has been used in combination with propylene glycol as a solvent for corticosteroids. The corticosteroid is dissolved in the solvent mixture to yield microdroplets that can then be dispersed in petrolatum.(1) Propylene carbonate has been used as a dispensing solvent in topical preparations.(2)

Propylene carbonate has also been used in hard gelatin capsules as a nonvolatile, stabilizing, liquid carrier. For formulations with a low dosage of active drug, a uniform drug content may be obtained by dissolving the drug in propylene carbonate then spraying this solution on to a solid carrier such as compressible sugar; the sugar may then be filled into hard gelatin capsules.(3)

Propylene carbonate may additionally be used as a solvent, at room and elevated temperatures, for many cellulose-based polymers and plasticizers. Propylene carbonate is also used in cosmetics.

8 Description

Propylene carbonate is a clear, colorless, mobile liquid, with a faint odor.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for propylene carbonate.

Test	USPNF 23
Identification	+
Specific gravity	1.203–1.210
pH (10% v/v aqueous solution)	6.0–7.5
Residue on ignition	⩽0.01%
Organic volatile impurities	+
Assay	99.0–100.5%

10 Typical Properties

Boiling point: 242°C
Flash point: 132°C
Freezing point: −49.2°C
Heat of combustion: 14.21 kJ/mol (3.40 kcal/mol)
Heat of vaporization: 55.2 kJ/mol (13.2 kcal/mol) at 150°C
Refractive index: n_D^{20} = 1.420–1.422
Solubility: practically insoluble in hexane; freely soluble in water. Miscible with acetone, benzene, chloroform, ethanol, ethanol (95%), and ether.
Specific heat: 2.57 J/g/°C (0.62 cal/g/°C) at 20°C
Vapor pressure: 4 Pa (0.03 mmHg) at 20°C.
Viscosity (dynamic): 2.5 mPa s (2.5 cP) at 25°C.

11 Stability and Storage Conditions

Propylene carbonate and its aqueous solutions are stable but may degrade in the presence of acids or bases, or upon heating; *see also* Section 12.

Store in a well-closed container in a cool, dry place.

12 Incompatibilities

Propylene carbonate hydrolyzes rapidly in the presence of strong acids and bases, forming mainly propylene oxide and carbon dioxide. Propylene carbonate can also react with primary and secondary amines to yield carbamates.

13 Method of Manufacture

Propylene carbonate may be prepared by the reaction of sodium bicarbonate with propylene chlorohydrin.(4)

14 Safety

Propylene carbonate is used as a solvent in oral and topical pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material.

In animal studies, propylene carbonate was found to cause tissue necrosis after parenteral administration.(5)

LD_{50} (mouse, oral): 20.7 g/kg
LD_{50} (mouse, SC): 15.8 g/kg
LD_{50} (rat, oral): 29 g/kg
LD_{50} (rat, SC): 11.1 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Propylene carbonate may be irritant to the eyes and mucous membranes. Eye protection and gloves are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (topical ointments). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

(*S*)-Propylene carbonate.

(*S*)-Propylene carbonate

Empirical formula: $C_4H_6O_3$
Molecular weight: 102.09
CAS number: [51260-39-0]
Specific rotation: $[\alpha]_D^{25} = -1.7°$ (0.92% v/v solution in ethanol)
Comments: the (*S*)-enantiomer of ±-propylene carbonate.(6)

18 Comments

The EINECS number for propylene carbonate is 203-572-1.

19 Specific References

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21 Authors

PJ Weller.

22 Date of Revision

9 August 2005.

Propylene Glycol

1 Nonproprietary Names

BP: Propylene glycol
JP: Propylene glycol
PhEur: Propylenglycolum
USP: Propylene glycol

2 Synonyms

1,2-Dihydroxypropane; E1520; 2-hydroxypropanol; methyl ethylene glycol; methyl glycol; propane-1,2-diol.

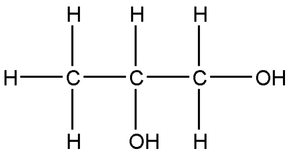
3 Chemical Name and CAS Registry Number

1,2-Propanediol [57-55-6]
(−)-1,2-Propanediol [4254-14-2]
(+)-1,2-Propanediol [4254-15-3]

4 Empirical Formula and Molecular Weight

$C_3H_8O_2$ 76.09

5 Structural Formula



$$\begin{array}{ccccccccc} & & H & & H & & H & & \\ & & \mid & & \mid & & \mid & & \\ H & - & C & - & C & - & C & - & OH \\ & & \mid & & \mid & & \mid & & \\ & & H & & OH & & H & & \end{array}$$

6 Functional Category

Antimicrobial preservative; disinfectant; humectant; plasticizer; solvent; stabilizer for vitamins; water-miscible cosolvent.

7 Applications in Pharmaceutical Formulation or Technology

Propylene glycol has become widely used as a solvent, extractant, and preservative in a variety of parenteral and nonparenteral pharmaceutical formulations. It is a better general solvent than glycerin and dissolves a wide variety of materials, such as corticosteroids, phenols, sulfa drugs, barbiturates, vitamins (A and D), most alkaloids, and many local anesthetics.

As an antiseptic it is similar to ethanol, and against molds it is similar to glycerin and only slightly less effective than ethanol.

Propylene glycol is commonly used as a plasticizer in aqueous film-coating formulations.

Propylene glycol is also used in cosmetics and in the food industry as a carrier for emulsifiers and as a vehicle for flavors in preference to ethanol, since its lack of volatility provides a more uniform flavor. *See* Table I.

Table I: Uses of propylene glycol.

Use	Dosage form	Concentration (%)
Humectant	Topicals	≈15
Preservative	Solutions, semisolids	15–30
Solvent or cosolvent	Aerosol solutions	10–30
	Oral solutions	10–25
	Parenterals	10–60
	Topicals	5–80

8 Description

Propylene glycol is a clear, colorless, viscous, practically odorless liquid with a sweet, slightly acrid taste resembling that of glycerin.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for propylene glycol.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Appearance	—	+	—
Specific gravity	1.035–1.040	1.035–1.040	1.035–1.037
Acidity	+	+	+
Water	⩽0.5%	⩽0.2%	⩽0.2%
Residue on ignition	⩽0.005%	—	⩽3.5 mg
Sulfated ash	—	⩽0.01%	—
Chloride	⩽0.007%	—	⩽0.007%
Sulfate	⩽0.002%	—	⩽0.006%
Heavy metals	⩽5 ppm	⩽5 ppm	⩽5 ppm
Organic volatile impurities	—	—	+
Refractive index	—	1.431–1.433	—
Oxidizing substances	—	+	—
Reducing substances	—	+	—
Arsenic	⩽2 ppm	—	—
Glycerin	+	—	—
Distilling range	184–189°C	—	—
Assay	—	—	⩾99.5%

10 Typical Properties

Autoignition temperature: 371°C
Boiling point: 188°C
Density: 1.038 g/cm^3 at 20°C
Flammability: upper limit, 12.6% v/v in air; lower limit, 2.6% v/v in air.
Flash point: 99°C (open cup)
Heat of combustion: 1803.3 kJ/mol (431.0 kcal/mol)
Heat of vaporization: 705.4 J/g (168.6 cal/g) at b.p.
Melting point: −59°C

Osmolarity: a 2.0% v/v aqueous solution is iso-osmotic with serum.

Refractive index: n_D^{20} = 1.4324

Specific rotation $[\alpha]_D^{20}$**:**

−15.0° (neat) for (*R*)-form;

+15.8° (neat) for (*S*)-form.

Solubility: miscible with acetone, chloroform, ethanol (95%), glycerin, and water; soluble at 1 in 6 parts of ether; not miscible with light mineral oil or fixed oils, but will dissolve some essential oils.

Specific heat: 2.47 J/g (0.590 cal/g) at 20°C

Surface tension: 40.1 mN/m (40.1 dynes/cm) at 25°C

Vapor density (relative): 2.62 (air = 1)

Vapor pressure: 9.33 Pa (0.07 mmHg) at 20°C

Viscosity (dynamic): 58.1 mPa s (58.1 cP) at 20°C

11 Stability and Storage Conditions

At cool temperatures, propylene glycol is stable in a well-closed container, but at high temperatures, in the open, it tends to oxidize, giving rise to products such as propionaldehyde, lactic acid, pyruvic acid, and acetic acid. Propylene glycol is chemically stable when mixed with ethanol (95%), glycerin, or water; aqueous solutions may be sterilized by autoclaving.

Propylene glycol is hygroscopic and should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

Propylene glycol is incompatible with oxidizing reagents such as potassium permanganate.

13 Method of Manufacture

Propylene is converted to chlorohydrin by chlorine water and hydrolyzed to 1,2-propylene oxide. With further hydrolysis, 1,2-propylene oxide is converted to propylene glycol.

14 Safety

Propylene glycol is used in a wide variety of pharmaceutical formulations and is generally regarded as a relatively nontoxic material. It is also used extensively in foods and cosmetics. Probably as a consequence of its metabolism and excretion, propylene glycol is less toxic than other glycols. Propylene glycol is rapidly absorbed from the gastrointestinal tract; there is also evidence that it is absorbed topically when applied to damaged skin. It is extensively metabolized in the liver, mainly to lactic and pyruvic acids and is also excreted unchanged in the urine.(1,2)

In topical preparations, propylene glycol is regarded as minimally irritant, although it is more irritant than glycerin. Some local irritation is produced upon application to mucous membranes or when it is used under occlusive conditions.(3) Parenteral administration may cause pain or irritation when used in high concentration.

Propylene glycol is estimated to be one-third as intoxicating as ethanol, with administration of large volumes being associated with adverse effects most commonly on the central nervous system, especially in neonates and children.(4–6) Other adverse reactions reported, though generally isolated, include: ototoxicity;(7) cardiovascular effects; seizures; and hyperosmolarity(8) and lactic acidosis, both of which occur most frequently in patients with renal impairment. Adverse effects are more likely to occur following consumption of large quantities of propylene glycol or on adminstration to neonates, children under 4 years of age, pregnant women, and patients with hepatic or renal failure. Adverse events may also occur in patients treated with disulfiram or metronidazole.(9)

On the basis of metabolic and toxicological data, the WHO has set an acceptable daily intake of propylene glycol at up to 25 mg/kg body-weight.(10) Formulations containing 35% propylene glycol can cause hemolysis in humans.

In animal studies, there has been no evidence that propylene glycol is teratogenic or mutagenic. Rats can tolerate a repeated oral daily dose of up to 30 mL/kg in the diet over 6 months, while the dog is unaffected by a repeated oral daily dose of 2 g/kg in the diet for 2 years.(11)

LD_{50} (mouse, IP): 9.72 g/kg(12)
LD_{50} (mouse, IV): 6.63 g/kg
LD_{50} (mouse, oral): 22.0 g/kg
LD_{50} (mouse, SC): 17.34 g/kg
LD_{50} (rat, IM): 0.01 g/kg
LD_{50} (rat, IP): 6.66 g/kg
LD_{50} (rat, IV): 6.42 g/kg
LD_{50} (rat, oral): 0.02 g/kg
LD_{50} (rat, SC): 22.5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Propylene glycol should be handled in a well-ventilated environment; eye protection is recommended. In the UK, the long-term (8-hour TWA) occupational exposure limit for propylene glycol vapor and particulates is 474 mg/m^3 (150 ppm) and 10 mg/m^3 for particulates.(13)

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (dental preparations, IM and IV injections, inhalations, ophthalmic, oral, otic, percutaneous, rectal, topical, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Propylene glycol alginate.

18 Comments

In addition to its uses as an excipient, propylene glycol is used in veterinary medicine as an oral glucogenic in ruminants.(14) A specification for potassium glycol is contained in the Food Chemicals Codex (FCC). The EINECS number for propylene glycol is 200-338-0.

19 Specific References

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21 Authors

SC Owen, PJ Weller.

22 Date of Revision

9 August 2005.

Propylene Glycol Alginate

1 Nonproprietary Names

USPNF: Propylene glycol alginate

2 Synonyms

Alginic acid, propylene glycol ester; E405; hydroxypropyl alginate; *Kelcoloid*; *Manucol ester*; *Pronova*; propane-1,2-diol alginate; *Protanal*; *TIC Pretested*.

3 Chemical Name and CAS Registry Number

Propylene glycol alginate [9005-37-2]

4 Empirical Formula and Molecular Weight

Propylene glycol alginate is a propylene glycol ester of alginic acid, a linear glycuronan polymer consisting of a mixture of β-(1→4)-D-mannosyluronic acid and α-(1→4)-L-gulosyluronic acid residues.

5 Structural Formula

See Section 4.

6 Functional Category

Antifoaming agent; emulsifying agent; flavoring agent; stabilizing agent; suspending agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Propylene glycol alginate is used as a stabilizing, suspending, gelling, and emulsifying agent in oral and topical pharmaceutical formulations. Typically, a concentration of 0.3–5% w/v is used, although this may vary depending upon the specific application and the grade of propylene glycol alginate used.

Propylene glycol alginate is also used in cosmetics and food products.

8 Description

Propylene glycol alginate occurs as a white to yellowish colored, practically odorless and tasteless, fibrous or granular powder.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for propylene glycol alginate.

Test	USPNF 23
Identification	+
Microbial limits	$\leqslant$200/g
Loss on drying	$\leqslant$20.0%
Ash	$\leqslant$10.0%
Arsenic	$\leqslant$3 ppm
Lead	$\leqslant$0.001%
Heavy metals	$\leqslant$0.004%
Free carboxyl groups	+
Esterified carboxyl groups	+
Assay (of alginates)	+

10 Typical Properties

Solubility: soluble in dilute organic acids and water, forming stable, viscous, colloidal solutions at pH 3. Depending upon the degree of esterification, propylene glycol alginate is also soluble in aqueous ethanol/water mixtures containing up to 60% w/w of ethanol (95%).

Viscosity (dynamic): the viscosity of aqueous solutions depends upon the grade of material used. Typically, a 1% w/v aqueous solution has a viscosity of 20–400 mPa s (20–400 cP). Viscosity may vary depending upon concentration, pH, temperature, or the presence of metal ions. *See also* Sodium Alginate.

11 Stability and Storage Conditions

Propylene glycol alginate is a stable material, although it will gradually become less soluble if stored at elevated temperatures for extended periods.

Propylene glycol alginate solutions are most stable at pH 3–6. In alkaline solutions, propylene glycol alginate is rapidly saponified. Alginate solutions are susceptible to microbial spoilage and should be sterilized or preserved with an antimicrobial preservative. However, sterilization processes may adversely affect the viscosity of propylene glycol alginate solutions, *see* Sodium Alginate.

The bulk material should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

—

13 Method of Manufacture

Alginic acid, extracted from brown seaweed, is reacted with propylene oxide to form propylene glycol alginate. Various grades may be obtained that differ in composition according to the degree of esterification and the percentage of free and neutralized carboxyl groups present in the molecule; complete esterification of alginic acid is impractical.

14 Safety

Propylene glycol alginate is used in oral and topical pharmaceutical formulations, cosmetics, and food products. It is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may be harmful. A study in five healthy male volunteers fed a daily intake of 175 mg/kg body-weight of propylene glycol alginate for 7 days, followed by a daily intake of 200 mg/kg body-weight of propylene glycol alginate for a further 16 days, showed no significant adverse effects.(1)

Inhalation of alginate dust may be irritant and has been associated with industrially related asthma in workers involved in alginate production. However, it appears that the cases of asthma were linked to exposure to seaweed dust rather than pure alginate dust.(2)

LD_{50} (hamster, oral): 7.0 g/kg(3)
LD_{50} (mouse, oral): 7.8 g/kg
LD_{50} (rabbit, oral): 7.6 g/kg
LD_{50} (rat, oral): 7.2 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Propylene glycol alginate may be irritant to the eyes or respiratory system if inhaled as dust; *see* Section 14. Eye protection, gloves, and a dust respirator are recommended. Propylene glycol alginate should be handled in a well-ventilated environment.

16 Regulatory Status

GRAS listed. Accepted in Europe for use as a food additive. Included in the FDA Inactive Ingredients Guide (oral preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Alginic acid; propylene glycol; sodium alginate.

18 Comments

A specification for propylene glycol alginate is contained in the Food Chemicals Codex (FCC).

See Alginic Acid and Sodium Alginate for further information.

19 Specific References

1 Anderson DM, Brydon WG, Eastwood MA, Sedgwick DM. Dietary effects of propylene glycol alginate in humans. *Food Addit Contam* 1991; **8**(3): 225–236.
2 Henderson AK, Ranger AF, Lloyd J, *et al*. Pulmonary hypersensitivity in the alginate industry. *Scott Med J* 1984; **29**(2): 90–95.
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20 General References

McDowell RH. New reactions of propylene glycol alginate. *J Soc Cosmet Chem* 1970; **21**: 441–457.

21 Authors

CK Tye.

22 Date of Revision

28 June 2005.

Propylparaben

1 Nonproprietary Names

BP: Propyl hydroxybenzoate
JP: Propyl parahydroxybenzoate
PhEur: Propylis parahydroxybenzoas
USPNF: Propylparaben

2 Synonyms

E216; 4-hydroxybenzoic acid propyl ester; *Nipasol M*; propagin; propyl *p*-hydroxybenzoate; *Propyl parasept*; *Solbrol P*; *Uniphen P-23*.

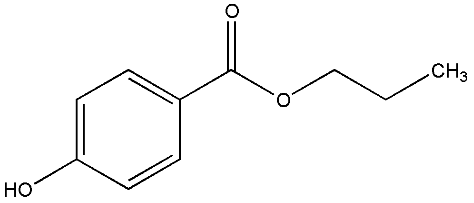
3 Chemical Name and CAS Registry Number

Propyl 4-hydroxybenzoate [94-13-3]

4 Empirical Formula and Molecular Weight

$C_{10}H_{12}O_3$ 180.20

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

Propylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations; *see* Table I.

It may be used alone, in combination with other paraben esters, or with other antimicrobial agents. It is one of the most frequently used preservatives in cosmetics.(1)

The parabens are effective over a wide pH range and have a broad spectrum of antimicrobial activity, although they are most effective against yeasts and molds; *see* Section 10.

Owing to the poor solubility of the parabens, the paraben salts, particularly the sodium salt, are frequently used in formulations. This may cause the pH of poorly buffered formulations to become more alkaline.

Propylparaben (0.02% w/v) together with methylparaben (0.18% w/v) has been used for the preservation of various parenteral pharmaceutical formulations; *see* Section 14.

See Methylparaben for further information.

Table I: Uses of propylparaben in pharmaceutical preparations.

Use	Concentration (%)
IM, IV, SC injections	0.005–0.2
Inhalation solutions	0.015
Intradermal injections	0.02–0.26
Nasal solutions	0.017
Ophthalmic preparations	0.005–0.01
Oral solutions and suspensions	0.01–0.02
Rectal preparations	0.02–0.01
Topical preparations	0.01–0.6
Vaginal preparations	0.02–0.1

8 Description

Propylparaben occurs as a white, crystalline, odorless, and tasteless powder.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for propylparaben.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Melting range	96.0–99.0°C	—	95.0–98.0°C
Acidity	—	+	—
Loss on drying	⩽0.5%	—	⩽0.5%
Residue on ignition	⩽0.1%	—	⩽0.05%
Sulfated ash	—	⩽0.1%	—
Appearance of solution	—	+	—
Chloride	⩽0.035%	—	—
Sulfate	⩽0.024%	—	—
Parahydroxy benzoic acid and salicylic acid	+	—	—
Heavy metals	⩽20 ppm	—	—
Related substances	—	+	—
Readily carbonizable substances	+	—	—
Organic volatile impurities	—	—	+
Assay (dried basis)	⩾99.0%	98.0–102.0%	99.0–100.5%

10 Typical Properties

Antimicrobial activity: propylparaben exhibits antimicrobial activity between pH 4–8. Preservative efficacy decreases with increasing pH owing to the formation of the phenolate anion. Parabens are more active against yeasts and molds than against bacteria. They are also more active against Gram-positive than against Gram-negative bacteria. The activity of the parabens increases with increasing chain length of the alkyl moiety; however, solubility decreases.

Activity may be improved by using combinations of parabens, as additive effects occur. Propylparaben has been used with methylparaben in parenteral preparations, and is used in combination with other parabens in topical and oral formulations. Activity has also been reported to be improved by the addition of other excipients; *see* Methylparaben.

Reported minimum inhibitory concentrations (MICs) for propylparaben are provided in Table III.(2)

Table III: Minimum inhibitory concentrations (MICs) for propylparaben in aqueous solution.(2)

Microorganism	**MIC (μg/mL)**
Aerobacter aerogenes ATCC 8308	1000
Aspergillus niger ATCC 9642	500
Aspergillus niger ATCC 10254	200
Bacillus cereus var. *mycoides* ATCC 6462	125
Bacillus subtilis ATCC 6633	500
Candida albicans ATCC 10231	250
Enterobacter cloacae ATCC 23355	1000
Escherichia coli ATCC 8739	500
Escherichia coli ATCC 9637	100
Klebsiella pneumoniae ATCC 8308	500
Penicillium chrysogenum ATCC 9480	125
Penicillium digitatum ATCC 10030	63
Proteus vulgaris ATCC 13315	250
Pseudomonas aeruginosa ATCC 9027	>1000
Pseudomonas aeruginosa ATCC 15442	>1000
Pseudomonas stutzeri	500
Rhizopus nigricans ATCC 6227A	125
Saccharomyces cerevisiae ATCC 9763	125
Salmonella typhosa ATCC 6539	500
Serratia marcescens ATCC 8100	500
Staphylococcus aureus ATCC 6538P	500
Staphylococcus epidermidis ATCC 12228	500
Trichophyton mentagrophytes	65

Boiling point: 295°C
Density (bulk): 0.426 g/cm^3
Density (tapped): 0.706 g/cm^3
Density(true): 1.288 g/cm^3
Dissociation constant: $pK_a = 8.4$ at 22°C
Flash point: 140°C
Partition coefficients: values for different vegetable oils vary considerably and are affected by the purity of the oil; *see* Table IV.

Table IV: Partition coefficients for propylparaben in vegetable oil and water.(3)

Solvent	**Partition coefficient oil : water**
Corn oil	58.0
Mineral oil	0.5
Peanut oil	51.8
Soybean oil	65.9

Refractive index: $n_D^{14} = 1.5049$
Solubility: *see* Table V.

Table V: Solubility of propylparaben in various solvents.(2)

Solvent	**Solubility at 20°C unless otherwise stated**
Acetone	Freely soluble
Ethanol (95%)	1 in 1.1
Ethanol (50%)	1 in 5.6
Ether	Freely soluble
Glycerin	1 in 250
Mineral oil	1 in 3330
Peanut oil	1 in 70
Propylene glycol	1 in 3.9
Propylene glycol (50%)	1 in 110
Water	1 in 4350 at 15°C
	1 in 2500
	1 in 225 at 80°C

11 Stability and Storage Conditions

Aqueous propylparaben solutions at pH 3–6 can be sterilized by autoclaving, without decomposition.(4) At pH 3–6, aqueous solutions are stable (less than 10% decomposition) for up to about 4 years at room temperature, while solutions at pH 8 or above are subject to rapid hydrolysis (10% or more after about 60 days at room temperature).(5)

See Table VI, for the predicted rate constants and half-lives at 25°C for propylparaben.(5)

Propylparaben should be stored in a well-closed container in a cool, dry place.

Table VI: Predicted rate constants and half-lives at 25°C for propylparaben dissolved in hydrochloric acid solution.

Initial pH of solution	**Rate constant $k \pm \sigma^{(a)}$ (h^{-1})**	**Half-life $t_{1/2} \pm \sigma^{(a)}$ (day)**
1	$(1.255 \pm 0.042) \times 10^{-4}$	230 ± 7.6
2	$(1.083 \pm 0.081) \times 10^{-5}$	2670 ± 200
3	$(8.41 \pm 0.96) \times 10^{-7}$	$34\,300 \pm 3900$
4	$(2.23 \pm 0.37) \times 10^{-7}$	$130\,000 \pm 22\,000$

(a) σ indicates the standard error.

The predicted amount of propylparaben remaining after autoclaving is given in Table VII.(5)

Table VII: Predicted amount of propylparaben dissolved in hydrochloric acid, after autoclaving.

Initial pH of solution	**Rate constant $k \pm \sigma^{(a)}$ (h^{-1})**	**Predicted residual amount after sterilization (%)**
1	$(4.42 \pm 0.10) \times 10^{-1}$	86.30 ± 0.30
2	$(4.67 \pm 0.19) \times 10^{-2}$	98.46 ± 0.06
3	$(2.96 \pm 0.24) \times 10^{-3}$	99.90 ± 0.01
4	$(7.8 \pm 1.1) \times 10^{-4}$	99.97 ± 0.004

(a) σ indicates the standard error.

12 Incompatibilities

The antimicrobial activity of propylparaben is reduced considerably in the presence of nonionic surfactants as a result of micellization.(6) Absorption of propylparaben by plastics has been reported, with the amount absorbed dependent upon the type of plastic and the vehicle.[7] Magnesium aluminum silicate, magnesium trisilicate, yellow iron oxide, and ultramarine blue have also been reported to absorb propylparaben, thereby reducing preservative efficacy.[8,9]

Propylparaben is discolored in the presence of iron and is subject to hydrolysis by weak alkalis and strong acids.

See also Methylparaben.

13 Method of Manufacture

Propylparaben is prepared by the esterification of *p*-hydroxybenzoic acid with *n*-propanol.

14 Safety

Propylparaben and other parabens are widely used as antimicrobial preservatives in cosmetics, food products, and oral and topical pharmaceutical formulations.

Propylparaben and methylparaben have been used as preservatives in injections and ophthalmic preparations; however they are now generally regarded as being unsuitable for these types of formulations owing to the irritant potential of the parabens.

Systemically, no adverse reactions to parabens have been reported, although they have been associated with hypersensitivity reactions. The WHO has set an estimated acceptable total daily intake for methyl, ethyl, and propyl parabens at up to 10 mg/kg body-weight.[10]

LD_{50} (mouse, IP): 0.2 g/kg[11]
LD_{50} (mouse, oral): 6.33 g/kg
LD_{50} (mouse, SC): 1.65 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Propylparaben may be irritant to the skin, eyes, and mucous membranes and should be handled in a well-ventilated environment. Eye protection, gloves, and a dust mask or respirator are recommended.

16 Regulatory Status

Propylparaben and methylparaben are affirmed GRAS direct food substances in the USA at levels up to 0.1%. All esters except the benzyl ester are allowed for injection in Japan.

In cosmetics, the EU and Brazil allow use of each paraben at 0.4%, but the total of all parabens may not exceed 0.8%. The upper limit in Japan is 1.0%.

Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IM, IV, and SC injections; inhalations; ophthalmic preparations; oral capsules, solutions, suspensions, and tablets; otic, rectal, topical, and vaginal preparations). Included in parenteral and nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Butylparaben; ethylparaben; methylparaben; propylparaben potassium; propylparaben sodium.

Propylparaben potassium

Empirical formula: $C_{10}H_{11}KO_3$
Molecular weight: 218.30
CAS number: [84930-16-5]
Synonyms: potassium propyl hydroxybenzoate; propyl 4-hydroxybenzoate potassium salt.

Propylparaben sodium

Empirical formula: $C_{10}H_{11}NaO_3$
Molecular weight: 202.20
CAS number: [35285-69-9]
Synonyms: E217; propyl 4-hydroxybenzoate sodium salt; sodium propyl hydroxybenzoate; soluble propyl hydroxybenzoate.
Appearance: white, odorless or almost odorless, hygroscopic crystalline powder.
Acidity/alkalinity: pH = 9.5–10.5 (0.1% w/v aqueous solution).
Solubility: 1 in 50 of ethanol (95%); 1 in 2 ethanol (50%); 1 in 1 of water; practically insoluble in fixed oils.
Comments: propylparaben sodium may be used instead of propylparaben because of its greater aqueous solubility. However, it may cause the pH of a formulation to become more alkaline.

18 Comments

A specification for propylparaben is contained in the Food Chemicals Codex (FCC). The EINECS number for propylparaben is 202-307-7.

See Methylparaben for further information and references.

19 Specific References

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21 Authors

R Johnson, R Steer.

22 Date of Revision

23 August 2005.

2-Pyrrolidone

1 Nonproprietary Names

None adopted.

2 Synonyms

γ-Aminobutyric acid lactam; 4-aminobutyric acid lactam; γ-aminobutyric lactam; γ-aminobutyrolactam; γ-butyrolactam; butyrolactam; 2-oxopyrrolidine; *2-Pyrol*; α-pyrrolidinone; pyrrolidone; α-pyrrolidone; *Soluphor P.*

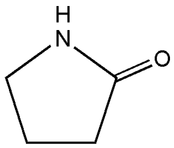
3 Chemical Name and CAS Registry Number

2-Pyrrolidinone [616-45-5]

4 Empirical Formula and Molecular Weight

C_4H_7NO 85.11

5 Structural Formula



6 Functional Category

Penetration enhancer; plasticizer; solvent; solubilizing agent.

7 Applications in Pharmaceutical Formulation or Technology

Pyrrolidones such as 2-pyrrolidone and *N*-methylpyrrolidone (*see* Section 17) are mainly used as solvents in veterinary injections.(1,2) They have also been suggested for use in human pharmaceutical formulations as solvents in parenteral, oral, and topical applications. In topical applications, pyrrolidones appear to be effective penetration enhancers.(1–7) Pyrrolidones have also been investigated for their application in controlled-release depot formulations.(8)

8 Description

2-Pyrrolidone occurs as a colorless or slightly colored liquid that solidifies at room temperature and has a characteristic odor.

9 Pharmacopeial Specifications

—

10 Typical Properties

Acidity/alkalinity: pH = 8.2–10.8 for a 10% v/v aqueous solution.

Boiling point: 245°C

Dipole moment: 2.3 Debye at 25°C

Enthalpy of vaporization: 48.21 ± 3.0 kJ/mol

Flash point (open cup): 54°C

Melting point: 2.6°C

Refractive index: n_D^{25} = 1.480–1.490

Solubility: miscible with ethanol (95%), propan-2-ol, and water. Also miscible with other organic solvents such as aromatic hydrocarbons.

Specific gravity: 1.11 at 25°C

Viscosity (dynamic): 13.3 mPa s (13.3 cP) at 25°C

11 Stability and Storage Conditions

2-Pyrrolidone is chemically stable and, if it is kept in unopened original containers, the shelf-life is approximately one year. 2-Pyrrolidone should be stored in a well-closed container protected from light and oxidation, at temperatures below 20°C.

12 Incompatibilities

2-Pyrrolidone is incompatible with oxidizing agents and strong acids.

13 Method of Manufacture

2-Pyrrolidone is prepared from butyrolactone by a Reppe process, in which acetylene is reacted with formaldehyde.

14 Safety

Pyrrolidones are mainly used in veterinary injections and have also been suggested for use in human oral, topical, and parenteral pharmaceutical formulations. In mammalian species, pyrrolidones are biotransformed to polar metabolites that are excreted via the urine.(9,10) 2-Pyrrolidone is mildly toxic by ingestion and subcutaneous routes; mutagenicity data have been reported.(11) 2-Pyrrolidone appears to be nonirritant when applied to skin and mucous membranes.(1)

LD_{50} (guinea pig, oral): 6.5 g/kg(11)
LD_{50} (rat, oral): 6.5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Some pyrrolidones in their pure state are considered toxic, corrosive, and flammable; contact with skin and eyes should be avoided. Vapors or sprays should not be inhaled. Suitable eye and skin protection and a respirator are recommended. When heated to decomposition, 2-pyrrolidone emits toxic fumes of NO_x.

16 Regulatory Status

—

17 Related Substances

N-Methylpyrrolidone.

N-Methylpyrrolidone

Synonyms: 1-methyl-2-pyrrolidinone; 1-methyl-5-pyrrolidinone; *N*-methyl-2-pyrrolidinone; methylpyrrolidone; *N*-methylpyrrolidonum; NMP; *Pharmasolve*; m-*Pyrol*.

Empirical formula: C_5H_9NO

Molecular weight: 99.14

CAS number: [872-50-4]

Description: *N*-methylpyrrolidone occurs as a clear, hygroscopic liquid with a mild amine odor.

Typical properties: ***Boiling point:*** 202°C

Dielectric constant: 32.2 at 25°C

Dipole moment: 4.9 Debye at 25°C

Enthalpy of evaporation: 43.82 ± 3.0 kJ/mol

Flash point (closed cup): 93°C

Flash point (open cup): 96°C

Freezing point: −24°C

Heat of combustion: 719 kcal/mol

Melting point: −17°C

Refractive index: $n_D^{25} = 1.4690$

Solubility: miscible with ethanol (95%), water, and most other organic solvents.

Specific gravity: 1.028 at 25°C

Surface tension: 40.7 mN/m (40.7 dyne/cm) at 25°C

Vapor pressure: 0.33 mmHg at 23.2°C; 5.00 mmHg at 65.0°C.

Viscosity: 1.65 mPa s (1.65 cP) at 25°C

Safety: *N*-methylpyrrolidone is considered a poison by the intravenous route. It is moderately toxic by ingestion, skin contact, and intraperitoneal routes. It is an experimental teratogen; mutagenicity data have been reported.(12)

LD_{50} (mouse, IP): 3.05 g/kg(12)
LD_{50} (mouse, IV): 0.155 g/kg
LD_{50} (mouse, oral): 5.13 g/kg
LD_{50} (rabbit, SC): 8.0 g/kg
LD_{50} (rat, IP): 2.472 g/kg
LD_{50} (rat, IV): 0.0805 g/kg
LD_{50} (rat, oral): 3.914 g/kg

Handling precautions: in the UK, the occupational exposure limits for *N*-methylpyrrolidone are 103 mg/m^3 (25 ppm) long-term (8-hour TWA) and 309 mg/m^3 (75 ppm) short-term (15 minutes).(13)

Comments: *N*-methylpyrrolidone is produced by the condensation of butyrolactone with methylamine. The EINECS number for *N*-methylpyrrolidone is 212-828-1. A specification for *N*-methylpyrrolidone is included in the PhEur 2005 and Japanese Pharmaceutical Excipients (JPE) 2004.(14)

18 Comments

The EINECS number for 2-pyrrolidone is 204-648-7.

19 Specific References

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20 General References

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21 Authors

RK Chang, AJ Shukla, Y Sun.

22 Date of Revision

26 August 2005.

Raffinose

1 Nonproprietary Names

None adopted.

2 Synonyms

Gossypose; melitose; melitriose; D-raffinose; D-(+)-raffinose.

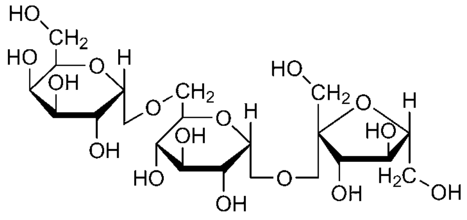
3 Chemical Name and CAS Registry Number

β-D-Fructofuranosyl-O-α-D-galactopyranosyl-(1→6)-α-D-glucopyranoside, anhydrous [512-69-6]
β-D-Fructofuranosyl-O-α-D-galactopyranosyl-(1→6)-α-D-glucopyranoside pentahydrate [17629-30-0]

4 Empirical Formula and Molecular Weight

$C_{18}H_{32}O_{16}$	504.44 (for anhydrous)
$C_{18}H_{32}O_{16}\cdot 5H_2O$	594.52 (for pentahydrate)

5 Structural Formula



D-Raffinose anhydrous

6 Functional Category

Blood substitute stabilizer; stabilizer for freeze-dried formulations; sucrose crystallization modifier.

7 Applications in Pharmaceutical Formulation or Technology

Raffinose is a trisaccharide carbohydrate that is used as a bulking agent, stabilizer, and water scavenger in freeze-drying.(1,2) It is also used as a crystallization inhibitor in sucrose solutions.(3–5)

8 Description

Raffinose is a white crystalline powder. It is odorless and has a sweet taste approximately 10% that of sucrose.(6)

9 Pharmacopeial Specifications

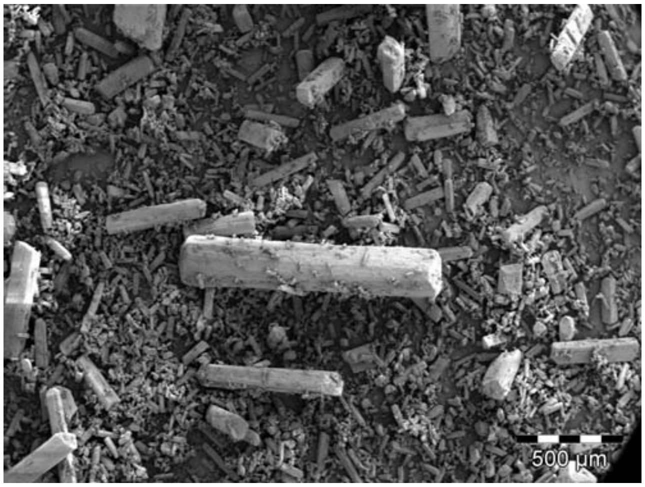
—

10 Typical Properties

Collapse temperature: –26°C(2)
Decomposition temperature: 130°C (pentahydrate)(7)
Density (bulk): 0.67 g/cm^3 (pentahydrate)
Density (tapped): 0.98 g/cm^3 (pentahydrate)
Density (true): 1.465 g/cm^3 (anhydrous)
Diffusion coefficient (infinite dilution): 0.33×10^{-5} cm^2/s (water at 15°C)(8)
Glass transition temperature: 114°C (amorphous)(9)
Heat of solution at infinite dilution (25°C): 52 kJ/mol (crystalline pentahydrate); –38 kJ/mol (amorphous)(1)
Melting point: 80°C (pentahydrate);(7) 118°C (anhydrous)(10)
Optical rotation: 105° (pentahydrate); 123° (anhydrous)(11)
Specific gravity: 1.465 (pentahydrate)(7)
Solubility in methanol: 0.10 g/mL(11)
Solubility in water: 0.14 g/mL(7)
Solubility: soluble 1 in 10 of methanol, in pyridine and 1 in 7.1 of water; slightly soluble in ethanol (95%); insoluble in diethyl ether.

The data for the crystal structure,(12,13) NMR structure,(14) powder x-ray diffraction pattern,(15) water vapor sorption isotherms, (15,16) glass transition temperature as a function of water,(15) heat capacity,(1) heat of solution properties,(1) vapor pressure,(17) and osmotic pressure(18) are described in the literature.

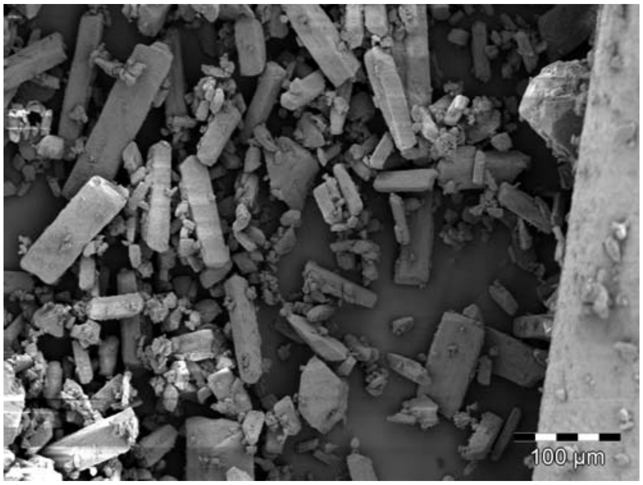
SEM: 1
Excipient: D-(+)-Raffinose pentahydrate
Manufacturer: Sigma-Aldrich (Lot No. 092K01211)
Magnification: 100×



11 Stability and Storage Conditions

Raffinose is stable under ordinary conditions of use and storage. Excessive heat should be avoided to prevent degradation. Thermal decomposition products are carbon monoxide and carbon dioxide.(19,20)

SEM: 2
Excipient: D-(+)-Raffinose pentahydrate
Manufacturer: Sigma-Aldrich (Lot No. 092K01211)
Magnification: 500×



12 Incompatibilities

Raffinose is incompatible with strong oxidizers.(21)

13 Method of Manufacture

Raffinose occurs naturally in Australian manna, cottonseed meal, and seeds of various food legumes. It can be isolated from beet sugar molasses through sucrose separation, seed-crystallization, and filtration.(13,22)

14 Safety

Raffinose is a naturally occurring trisaccharide investigated for use in freeze-dried pharmaceutical formulations. It occurs in a number of plants that are consumed widely (*see* Section 13).

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Gloves and safety glasses are recommended. Dust generation should be kept to reasonable levels to avoid ignition or explosion. Short-term exposure has caused respiratory and eye irritation. Long-term exposure has shown adverse reproductive effects in animals. No occupational exposure limits have been established. Dust or air mixtures may ignite or explode.(19,20)

16 Regulatory Status

Raffinose is a naturally occurring trisaccharide and is consumed as part of a normal diet.

17 Related Substances

Raffinose is composed of three monosaccharides: galactose, glucose, and fructose. It shares related structures with sucrose and melibiose. It is also related to stachyose, which possesses an additional (1→6)-linked α-D-galactopyranosyl unit.

Two solvated forms(22) and an amorphous form(14,23,24) of raffinose can be synthesized.

18 Comments

Raffinose has been shown to accumulate in organisms that can survive extreme desiccation, and has therefore been examined as an excipient in stabilizing co-lyophilized protein and labile preparations during storage at elevated temperatures.(25,26)

When exposed to elevated relative humidity (RH) of 75% at 25°C, raffinose has been shown to form different hydrate levels.(27)

Raffinose is indigestible by humans because of a lack of an α-galactosidase and undergoes fermentation in the colon, causing production of carbon dioxide, hydrogen, and methane gases.(10)

19 Specific References

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20 General References

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21 Authors

BC Hancock, MP Mullarney.

22 Date of Revision

25 August 2005.

Saccharin

1 Nonproprietary Names

BP: Saccharin
PhEur: Saccharinum
USPNF: Saccharin

2 Synonyms

1,2-Benzisothiazolin-3-one 1,1-dioxide; benzoic sulfimide; benzosulfimide; 1,2-dihydro-2-ketobenzisosulfonazole; 2,3-dihydro-3-oxobenzisosulfonazole; E954; *Garantose*; gluside; *Hermesetas*; sacarina; saccharin insoluble; *o*-sulfobenzimide; *o*-sulfobenzoic acid imide.

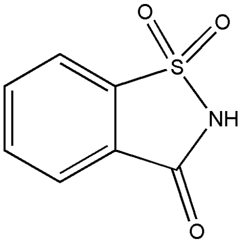
3 Chemical Name and CAS Registry Number

1,2-Benzisothiazol-3(2*H*)-one 1,1-dioxide [81-07-2]

4 Empirical Formula and Molecular Weight

$C_7H_5NO_3S$ 183.18

5 Structural Formula



6 Functional Category

Sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

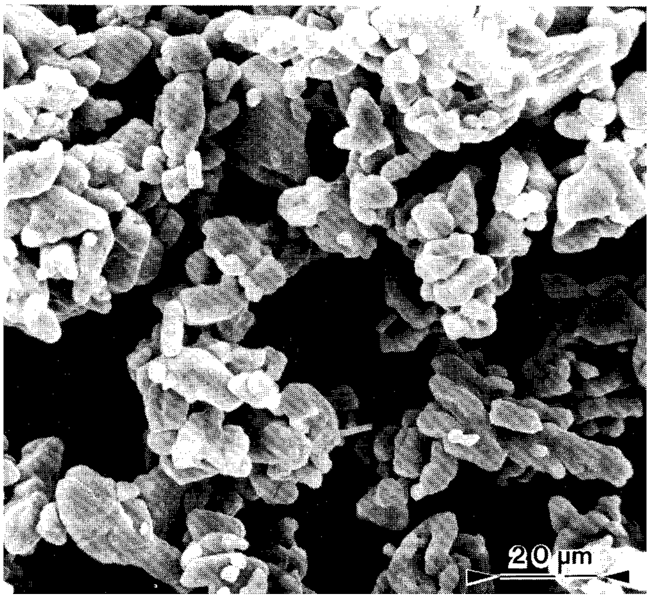
Saccharin is an intense sweetening agent used in beverages, food products, table-top sweeteners, and oral hygiene products such as toothpastes and mouthwashes. In oral pharmaceutical formulations, it is used at a concentration of 0.02–0.5% w/w. It has been used in chewable tablet formulations as a sweetening agent.[1,2]

Saccharin can be used to mask some unpleasant taste characteristics or to enhance flavor systems. Its sweetening power is approximately 500 times that of sucrose.

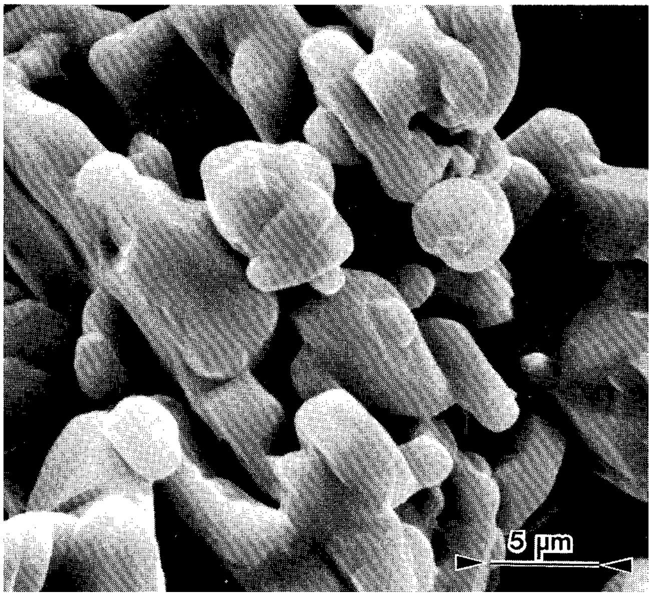
8 Description

Saccharin occurs as odorless white crystals or a white crystalline powder. It has an intensely sweet taste, with a metallic aftertaste that at normal levels of use can be detected by approximately 25% of the population.

SEM: 1
Excipient: Saccharin
Magnification: 600×



SEM: 2
Excipient: Saccharin
Magnification: 2400×



9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for saccharin.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Melting range	226–230°C	226–230°C
Loss on drying	⩽1.0%	⩽1.0%
Residue on ignition	—	⩽0.2%
Sulfated ash	⩽0.1%	—
Toluenesulfonamides	+	⩽0.0025%
Selenium	—	⩽0.003%
Heavy metals	⩽20 ppm	⩽0.001%
Readily carbonizable substances	—	+
Benzoic and salicylic acids	—	+
Organic volatile impurities	—	+
Related substances	—	—
Assay (dried basis)	98.0–101.0%	98.0–101.0%

10 Typical Properties

Acidity/alkalinity: pH = 2.0 (0.35% w/v aqueous solution)
Density (bulk): 0.7–1.0 g/cm^3
Density (tapped): 0.9–1.2 g/cm^3
Dissociation constant: pK_a = 1.6 at 25°C
Heat of combustion: 3644.3 kJ/mol (871 kcal/mol)
Moisture content: 0.1%
Solubility: readily dissolved by dilute ammonia solutions, alkali hydroxide solutions, or alkali carbonate solutions (with the evolution of carbon dioxide). *See* Table II.

Table II: Solubility of saccharin.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	1 in 12
Chloroform	Slightly soluble
Ethanol (95%)	1 in 31
Ether	Slightly soluble
Glycerin	1 in 50
Water	1 in 290
	1 in 25 at 100°C

11 Stability and Storage Conditions

Saccharin is stable under the normal range of conditions employed in formulations. In the bulk form it shows no detectable decomposition and only when it is exposed to a high temperature (125°C) at a low pH (pH 2) for over 1 hour does significant decomposition occur. The decomposition product formed is (ammonium-*o*-sulfo)benzoic acid.(3)

Saccharin should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Saccharin can react with large molecules, resulting in a precipitate being formed.

13 Method of Manufacture

Saccharin is prepared from toluene by a series of reactions known as the Remsen–Fahlberg method. Toluene is first reacted with chlorosulfonic acid to form *o*-toluenesulfonyl chloride, which is reacted with ammonia to form the sulfonamide. The methyl group is then oxidized with dichromate, yielding *o*-sulfamoylbenzoic acid, which forms the cyclic imide saccharin when heated.

An alternative method involves a refined version of the Maumee process. Methyl anthranilate is initially diazotized to form 2-carbomethoxybenzenediazonium chloride; sulfonation followed by oxidation then yields 2-carbomethoxybenzenesulfonyl chloride. Amidation of this material, followed by acidification, forms insoluble acid saccharin.

14 Safety

There has been considerable controversy concerning the safety of saccharin, which has led to extensive studies since the mid-1970s.

Two-generation studies in rats exposed to diets containing 5.0–7.5% total saccharin (equivalent to 175 g daily in humans) suggested that the incidence of bladder tumors was significantly greater in saccharin-treated males of the second generation than in controls.(4,5) Further experiments in rats suggested that a contaminant of commercial saccharin, *o*-toluene sulfonamide, might also account for carcinogenic effects. In view of these studies, a ban on the use of saccharin was proposed in several countries. However, in 1977 a ban by the FDA led to a Congressional moratorium that permitted the continued use of saccharin in the USA.

From the available data it now appears that the development of tumors is a sex-, species-, and organ-specific phenomenon and extensive epidemiological studies have shown that saccharin intake is not related to bladder cancer in humans.(6,7)

The WHO has set a temporary acceptable daily intake for saccharin, including its calcium, potassium, and sodium salts, at up to 2.5 mg/kg body-weight.(8) In the UK, the Committee on Toxicity of Chemicals in Food, Consumer Products, and the Environment (COT) has set an acceptable daily intake for saccharin and its calcium, potassium, and sodium salts (expressed as saccharin sodium) at up to 5 mg/kg body-weight.(9)

Adverse reactions to saccharin, although relatively few in relation to its widespread use, include: urticaria with pruritus following ingestion of saccharin-sweetened beverages(10) and photosensitization reactions.(11)

LD_{50} (mouse, oral): 17.5 g/kg(12)
LD_{50} (rat, IP): 7.10 g/kg
LD_{50} (rat, oral): 14.2 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended.

16 Regulatory Status

Accepted for use as a food additive in Europe. Note that the EU number ‘E954’ is applied to both saccharin and saccharin salts. Included in the FDA Inactive Ingredients Guide (oral solutions, syrups, tablets, and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Alitame; saccharin ammonium; saccharin calcium; saccharin sodium.

Saccharin ammonium

Empirical formula: $C_7H_8N_2O_3S$
Molecular weight: 200.2
CAS number: [6381-61-9]

Saccharin calcium

Empirical formula: $C_{14}H_8CaN_2O_6S_2 \cdot 3H_2O$
Molecular weight: 467.48
CAS number:
[6381-91-5] for the hydrated form
[6485-34-3] for the anhydrous form
Synonyms: *Syncal CAS*.
Appearance: white, odorless crystals or crystalline powder with an intensely sweet taste.
Solubility: 1 in 4.7 ethanol (95%); 1 in 2.6 of water.

18 Comments

The perceived intensity of sweeteners relative to sucrose depends upon their concentration, temperature of tasting, and pH, and on the flavor and texture of the product concerned.

Intense sweetening agents will not replace bulk, textural, or preservative characteristics of sucrose if sucrose is removed from a formulation.

Synergistic effects for combinations of sweeteners have been reported. Saccharin is often used in combination with cyclamates and aspartame since the saccharin content may be reduced to minimize any aftertaste. A specification for saccharin is contained in the Food Chemicals Codex (FCC).

The EINECS number for saccharin is 201-321-0.

19 Specific References

1 Suzuki H, Onishi H, Hisamatsu S, *et al*. Acetaminophen-containing chewable tablets with suppressed bitterness and improved oral feeling. *Int J Pharm* 2004; **278**(1): 57–61.
2 Mullarney MP, Hancock BC, Carlson GT, *et al*. The powder flow and compact mechanical properties of sucrose and three high-density sweetners used in chewable tablets. *Int J Pharm* 2003; **257**(1–2): 227–236.
3 DeGarmo O, Ashworth GW, Eaker CM, Munch RH. Hydrolytic stability of saccharin. *J Am Pharm Assoc (Sci)* 1952; **41**: 17–18.
4 Arnold DL, Moodie CA, Grice HC, *et al*. Long-term toxicity of *ortho*-toluenesulfonamide and sodium saccharin in the rat. *Toxicol Appl Pharmacol* 1980; **52**: 113–152.
5 Arnold DL. Two-generation saccharin bioassays. *Environ Health Perspect* 1983; **50**: 27–36.
6 Council on Scientific Affairs. Saccharin: review of safety issues. *J Am Med Assoc* 1985; **254**: 2622–2624.
7 Morgan RW, Wong O. A review of epidemiological studies on artificial sweeteners and bladder cancer. *Food Chem Toxicol* 1985; **23**: 529–533.
8 FAO/WHO. Evaluation of certain food additives and contaminants. Twenty-eighth report of the FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1984; No. 710.
9 Food Advisory Committee. FAC further advice on saccharin. FdAC/REP/9. London: MAFF, 1990.
10 Miller R, White LW, Schwartz HJ. A case of episodic urticaria due to saccharin ingestion. *J Allergy Clin Immunol* 1974; **53**: 240–242.
11 Gordon HH. Photosensitivity to saccharin. *J Am Acad Dermatol* 1983; **8**: 565.
12 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 3277.

20 General References

Anonymous. Saccharin is safe. *Chem Br* 2001; **37**(4): 18.
Lindley MG. Sweetener markets, marketing and product development. In: Marie S, Piggott JR, eds. *Handbook of Sweeteners*. Glasgow: Blackie, 1991: 186.
Zubair MU, Hassan MMA. Saccharin. In: Florey K, ed. *Analytical Profiles of Drug Substances*, vol. **13**. Orlando, FL: Academic Press, 1984: 487–519.

21 Authors

SC Owen.

22 Date of Revision

11 August 2005.

Saccharin Sodium

1 Nonproprietary Names

BP: Saccharin sodium
JP: Saccharin sodium
PhEur: Saccharinum natricum
USP: Saccharin sodium

2 Synonyms

1,2-Benzisothiazolin-3-one 1,1-dioxide, sodium salt; *Crystallose*; E954; sodium *o*-benzosulfimide; soluble gluside; soluble saccharin; sucaryl sodium.

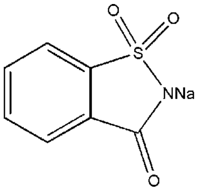
3 Chemical Name and CAS Registry Number

1,2-Benzisothiazol-3(2*H*)-one 1,1-dioxide, sodium salt
[6155-57-3] for the dihydrate
[128-44-9] for the anhydrous material
See also Section 8.

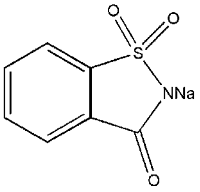
4 Empirical Formula and Molecular Weight

$C_7H_4NNaO_3S$	205.16
$C_7H_4NNaO_3S\cdot\frac{2}{3}H_2O$ (84%)	217.24
$C_7H_4NNaO_3S\cdot 2H_2O$ (76%)	241.19

5 Structural Formula



$\cdot 2H_2O$ 76% saccharin sodium (dihydrate)



$\cdot \frac{2}{3} H_2O$ 84% saccharin sodium

6 Functional Category

Sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

Saccharin sodium is an intense sweetening agent used in beverages, food products, table-top sweeteners,(1) and pharmaceutical formulations such as tablets, powders, medicated confectionery, gels, suspensions, liquids, and mouthwashes;(2) *see* Table I. It is also used in vitamin preparations.

Saccharin sodium is considerably more soluble in water than saccharin, and is more frequently used in pharmaceutical formulations. Its sweetening power is approximately 300 times that of sucrose. Saccharin sodium enhances flavor systems and may be used to mask some unpleasant taste characteristics.

Injection of saccharin sodium has been used to measure the arm-to-tongue circulation time.

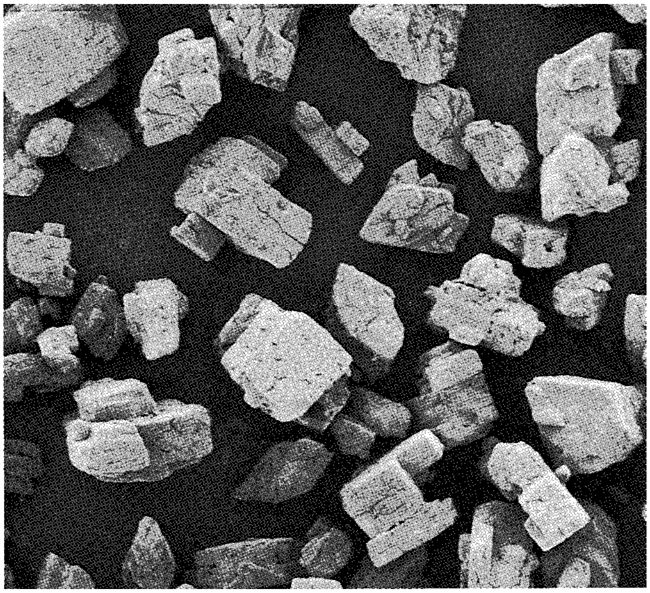
Table I: Uses of saccharin sodium.

Use	Concentration (%)
Dental paste/gel	0.12–0.3
IM/IV injections	0.9
Oral solution	0.075–0.6
Oral syrup	0.04–0.25

8 Description

Saccharin sodium occurs as a white, odorless or faintly aromatic, efflorescent, crystalline powder. It has an intensely sweet taste, with a metallic aftertaste that at normal levels of use can be detected by approximately 25% of the population. Saccharin sodium can contain variable amounts of water.

SEM: 1
Excipient: Saccharin sodium
Magnification: 35×
Voltage: 5 kV



9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for saccharin sodium.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	+	+	—
Clarity and color of solution	+	+	—
Acidity or alkalinity	+	+	+
Water	⩽15.0%	⩽15.0%	⩽15.0%
Benzoate and salicylate	+	—	+
Arsenic	⩽2 ppm	—	—
Selenium	—	—	⩽0.003%
Acidity or alkalinity	+	+	+
Toluenesulfonamides	+	+	+
Heavy metals ⩽0.001%		⩽20 ppm	⩽20 ppm
Readily carbonizable substances	+	—	+
Organic volatile impurities	—	—	+
Assay (anhydrous basis)	⩾98.0%	99.0–101.0%	98.0–101.0%

10 Typical Properties

Unless stated, data refer to either 76% or 84% saccharin sodium.

Acidity/alkalinity: pH = 6.6 (10% w/v aqueous solution)

Density (bulk):
0.8–1.1 g/cm^3 (76% saccharin sodium);
0.86 g/cm^3 (84% saccharin sodium).

Density (particle): 1.70 g/cm^3 (84% saccharin sodium)

Density (tapped):
0.9–1.2 g/cm^3 (76% saccharin sodium);
0.96 g/cm^3 (84% saccharin sodium).

Melting point: decomposes upon heating.

Moisture content: saccharin sodium 76% contains 14.5% w/w water; saccharin sodium 84% contains 5.5% w/w water. During drying, water evolution occurs in two distinct phases. The 76% material dries under ambient conditions to approximately 5.5% moisture (84% saccharin sodium); the remaining moisture is then removed only by heating.

Solubility: *see* Table III.

Table III: Solubility of saccharin sodium.

Solvent	Solubility at 20°C unless otherwise stated
Buffer solutions:	
pH 2.2 (phthalate)	1 in 1.15
	1 in 0.66 at 60°C
pH 4.0 (citrate–phosphate)	1 in 1.21
	1 in 0.69 at 60°C
pH 7.0 (citrate–phosphate)	1 in 1.21
	1 in 0.66 at 60°C
pH 9.0 (borate)	1 in 1.21
	1 in 0.69 at 60°C
Ethanol	1 in 102
Ethanol (95%)	1 in 50
Propylene glycol	1 in 3.5
Propan-2-ol	Practically insoluble
Water	1 in 1.2

Specific surface area: 0.25 m^2/g

11 Stability and Storage Conditions

Saccharin sodium is stable under the normal range of conditions employed in formulations. Only when it is exposed to a high temperature (125°C) at a low pH (pH 2) for over 1 hour does significant decomposition occur. The 84% grade is the most stable form of saccharin sodium since the 76% form will dry further under ambient conditions.

Saccharin sodium should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

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13 Method of Manufacture

Saccharin is produced by the oxidation of *o*-toluene sulfonamide by potassium permanganate in a solution of sodium hydroxide. Acidification of the solution precipitates saccharin, which is then dissolved in water at 50°C and neutralized by addition of sodium hydroxide. Rapid cooling of the solution initiates crystallization of saccharin sodium from the liquors.

14 Safety

There has been considerable controversy concerning the safety of saccharin and saccharin sodium in recent years; however, it is now generally regarded as a safe, intense sweetener. *See* Saccharin for further information.

The WHO has set a temporary acceptable daily intake of up to 2.5 mg/kg body-weight for saccharin, including its salts.(3) In the UK, the Committee on Toxicity of Chemicals in Food, Consumer Products, and the Environment (COT) has set an acceptable daily intake for saccharin and its salts (expressed as saccharin sodium) at up to 5 mg/kg body-weight.(4)

LD_{50} (mouse, oral): 17.5 g/kg(5)
LD_{50} (rat, IP): 7.1 g/kg
LD_{50} (rat, oral): 14.2 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended.

16 Regulatory Status

Accepted for use as a food additive in Europe; 'E954' is applied to both saccharin and saccharin salts. Included in the FDA Inactive Ingredients Guide (buccal and dental preparations; IM and IV injections; oral and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Alitame; saccharin.

18 Comments

The perceived intensity of sweeteners relative to sucrose depends upon their concentration, temperature of tasting, and pH, and on the flavor and texture of the product concerned.

Intense sweetening agents will not replace bulk, textural, or preservative characteristics of sugar if sugar is removed from a formulation.

Synergistic effects for combinations of sweeteners have been reported. Saccharin sodium is often used in combination with cyclamates and aspartame since the saccharin sodium content may be reduced to minimize any aftertaste.

19 Specific References

1 Kloesel L. Sugar substitutes. *Int J Pharm Compound* 2000; **4**(2): 86–87.
2 Ungphaiboon S, Maitani Y. *In vitro* permeation studies of triamcinolone acetonide mouthwashes. *Int J Pharm* 2001; **220**(1–2): 111–117.
3 FAO/WHO. Evaluation of certain food additives and contaminants. Twenty-eighth report of the FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1984; No. 710.
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5 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 3277.

See Saccharin for further references.

20 General References

Anonymous. Saccharin is safe. *Chem Br* 2001; **37**(4): 18.
Lindley MG. Sweetener markets, marketing and product developments. In: Marie S, Piggott JR, eds. *Handbook of Sweeteners*. Glasgow: Blackie, 1991: 186.

21 Authors

SC Owen.

22 Date of Revision

11 August 2005.

Saponite

1 Nonproprietary Names

None adopted.

2 Synonyms

Afrodit; aluminum-saponite; auxite; cathkinite; ferroan saponite; griffithite; licianite; lucianite.

3 Chemical Name and CAS Registry Number

Saponite [1319-41-1]

4 Empirical Formula and Molecular Weight

$(Ca_{0.5}Na)_{0.3}(Mg,Fe^{2+})_3(Si,Al)_4O_{10}(OH)_2{\cdot}4H_2O$ ≈480

Saponite is a naturally occurring phyllosilicate clay of the smectite (montmorillonite) group. It is a magnesium-rich hydrated aluminum silicate and is present as a component of some commercial magnesium aluminum silicate clays. Saponite is a mineral with an approximate empirical formula owing to the variability in cation substitution; *see* Table I.

Table I: Approximate composition of saponite based on chemical analysis.

Component	Wt %
SiO_2	37.5
Al_2O_3	10.6
MgO	18.9
CaO	1.2
Na_2O	0.65
FeO	11.2
H_2O	18.8

5 Structural Formula

Saponite is a natural mineral clay that is a hydrous silicate of aluminum and magnesium. It occurs in soft, amorphous masses in the cavities of certain rocks.

Saponite is composed of two tetrahedral layers formed by phylosilicate sheets and one octahedral layer. Common impurities include manganese, nickel, phosphorus, potassium, and titanium.

See Section 4.

6 Functional Category

Adsorbent; emulsifying agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Saponite is a colloidal material present in various naturally occurring clays such as magnesium aluminum silicates(1) and is therefore suitable for use in pharmaceutical formulation applications as an adsorbent, viscosity-increasing agent, suspending agent, or as an oil-in-water emulsifying agent. It is a swelling clay with a low cation exchange capacity, and when mixed with water it displays thixotropic properties. Saponite is similar to bentonite, and has the capacity to adsorb drugs through cationic exchange.(2) Drug–saponite adsorbates show a slight reduction in dissolution rate.(2) Saponite is useful in the formulation of gastrointestinal X-ray contrast agents(3) and formulations designed for sustained drug delivery to the gastrointestinal tract.(4)

8 Description

Saponite occurs as a white to off-white, dull powder composed of fine-grained crystals of colloidal size. The material is greasy or soapy to the touch and swells on the addition of water.

9 Pharmacopeial Specifications

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10 Typical Properties

Density (true): 2.67 g/cm^3

Crystal data: monoclinic; $a = 5.3$, $b = 9.14$, $c = 16.9$, $\beta \approx 97°$.

Hardness (Mohs): 1–2

11 Stability and Storage Conditions

Saponite is a stable material and should be stored in a cool, dry place.

12 Incompatibilities

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13 Method of Manufacture

Naturally occurring saponite is mined from deposits in various localities around the world.

14 Safety

Saponite is a natural clay mineral that is not acutely toxic; therefore, no toxicity values have been established. However, it may contain small amounts of crystalline silica in the form of quartz. Chronic exposure to crystalline silica can have adverse effects on the respiratory system. EU labeling states the material is not classified as dangerous.

Saponite dust can be irritating to the respiratory tract and eyes. Contact with this material may cause drying of the skin.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material being handled. Avoid generating and breathing dust and use eye protection. For dusty conditions, eye protection, gloves, and a dust mask are recommended. The occupational exposure limits for saponite are 5 mg/m^3 (respirable) PEL-TWA, 3 mg/m^3 (respirable) TLV-TWA, and 10 mg/m^3 (inhalable) dust TLV-TWA.

16 Regulatory Status

Reported in the EPA TSCA Inventory.

17 Related Substances

Attapulgite; bentonite; kaolin; hectorite; magnesium aluminum silicate; talc.

18 Comments

The EINECS number for saponite is 215-289-0.

19 Specific References

1 Browne JE, Feldkamp JR, White JL, Hem SL. Characterization and adsorptive properties of pharmaceutical grade clays. *J Pharm Sci* 1980; **69**(7): 816–823.

2 El-Gindy GA, Ali AS, El-Shinnawi OM. Preparation and formulation of sustained-release terbutaline sulphate microcapsules. *Bull Pharm Sci Assiut Univ* 2000; **23**(1): 55–63.

3 Ruddy SB, Eickhoff WM, Liversidge G, Cooper ER. Formulations of oral gastrointestinal therapeutic agents in combination with pharmaceutically acceptable clays. International Patent WO96/2096; 1996.

4 Ruddy SB, McIntire GL, Roberts ME, Caulifield TJ, Cooper ER. X-ray contrast compositions containing iodoaniline derivatives and pharmaceutically acceptable clays. United States Patent No. 5,424,056; 1995.

20 General References

Cormleyu I, Addison J. The *in vitro* cytotoxicity of some standard clay mineral dusts of respirable size. *Clay Miner* 1983; **18**(2): 153–163.

Polon JA. Mechanisms of thickening by inorganic agents. *J Soc Cosmet Chem* 1970; **21**: 347–363.

Post JL. Saponite from near Ballarat, California. *Clays Clay Miner* 1984; **32**: 147–153.

Viseras C, Lopez-Galindo A. Characteristics of pharmaceutical grade phylosilicate powders. *Pharm Dev Technol* 2000; **5**(1): 47–52.

21 Authors

PE Luner.

22 Date of Revision

18 August 2005.

Sesame Oil

1 Nonproprietary Names

BP: Refined sesame oil
JP: Sesame oil
PhEur: Sesami oleum raffinatum
USPNF: Sesame oil

2 Synonyms

Benne oil; gingelly oil; gingili oil; jinjili oil; *Lipovol SES*; teel oil.

3 Chemical Name and CAS Registry Number

Sesame oil [8008-74-0]

4 Empirical Formula and Molecular Weight

A typical analysis of refined sesame oil indicates the composition of the acids, present as glycerides, to be: arachidic acid 0.8%; linoleic acid 40.4%; oleic acid 45.4%; palmitic acid 9.1%; and stearic acid 4.3%. Sesamin, a complex cyclic ether, and sesamolin, a glycoside, are also present in small amounts.

Note that other reported analyses may vary slightly from that above.(1)

The monographs for Sesame Oil in the USPNF 23 and Refined Sesame Oil in the PhEur 2005 specify the acceptable range of eight triglycerides found in sesame oil.

5 Structural Formula

See Section 4.

6 Functional Category

Oleaginous vehicle; solvent.

7 Applications in Pharmaceutical Formulation or Technology

The major use of sesame oil in pharmaceutical formulations is as a solvent in the preparation of sustained-release intramuscular injections of steroids, such as estradiol valerate, hydroxyprogesterone caproate, testosterone enanthate, and nandrolone decanoate,(2) or other oil-soluble drug substances, such as, the decanoates or enanthate esters of fluphenazine. The disappearance of sesame oil from the injection site, following subcutaneous or intramuscular administration to pigs, has been reported to have a half-life of about 23 days.(3)

Sesame oil may be used as a solvent in the preparation of subcutaneous injections,(4) oral capsules,(5,6) rectal suppositories,(7) and ophthalmic preparations;(8) it may also be used in the formulation of suspensions(9) and emulsions.(9–11) Multiple-emulsion formulations, in which sesame oil was one of the oil phases incorporated, have been investigated as a prolonged-release system for rifampicin;(12) microemulsions containing sesame oil have been prepared for the transdermal delivery of ketoprofen.(13) Sesame oil has also been used in the preparation of liniments, pastes, ointments, and soaps. A sesame paste (tahini), composed of crushed sesame seeds in sesame oil, has been investigated as a novel suspending agent.(14)

Sesame oil is additionally used as an edible oil and in the preparation of oleomargarine.

8 Description

Refined sesame oil is a clear, pale-yellow colored liquid with a slight, pleasant odor and a bland taste. It solidifies to a soft mass at about −4°C.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sesame oil.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Specific gravity	0.914–0.921	0.919	0.916–0.921
Refractive index at 20°C	—	1.470–1.476	—
Heavy metals	—	—	≤0.001%
Cottonseed oil	—	+	+
Solidification range of fatty acids	—	—	20–25°C
Free fatty acids	—	—	+
Acid value	≤0.2	≤0.6	—
	—	≤0.3[a]	—
Iodine value	103–118		103–116
Peroxide value	—	≤10.0	—
	—	≤5.0[a]	—
Saponification value	187–194	—	188–195
Unsaponifiable matter	≤2.0%	≤2.0%	≤1.5%
Composition of triglycerides	—	+	+
Alkaline impurities	—	+	—
Organic volatile impurities	—	—	+
Water	—	≤0.05%[a]	—

[a] In sesame oil intended for parenteral use.

10 Typical Properties

Density: 0.916–0.920 g/cm^3
Flash point: 338°C (open cup)
Freezing point: −5°C
Refractive index: n_D^{40} = 1.4650–1.4665
Solubility: insoluble in water; practically insoluble in ethanol (95%); miscible with carbon disulfide, chloroform, ether, hexane, and light petroleum.
Specific rotation $[\alpha]_D^{25}$**:** +1° to +9°
Viscosity (dynamic): 43 mPa s (43 cP)

11 Stability and Storage Conditions

Sesame oil is more stable than most other fixed oils and does not readily become rancid; this has been attributed to the antioxidant effect of some of its characteristic constituents. The PhEur 2005 permits the addition of a suitable antioxidant to sesame oil.

Sesame oil may be sterilized by aseptic filtration or dry heat. It has been reported that suitable conditions for the sterilization of injections containing sesame oil are a temperature of 170°C for 2 hours; it has been suggested that 150°C for 1 hour is inadequate.(15) However, it has been demonstrated that dry heat sterilization of sesame oil at 150°C for 1 hour was sufficient to kill all added *Bacillus subtilis* spores.(16)

Sesame oil should be stored in a well-filled, airtight, light-resistant container, at a temperature not exceeding 40°C. Sesame oil intended for use in the manufacture of parenteral dosage forms should be stored under an inert gas in an airtight glass container.

12 Incompatibilities

Sesame oil may be saponified by alkali hydroxides.

13 Method of Manufacture

Sesame oil is obtained from the ripe seeds of one or more cultivated varieties of *Sesamum indicum* Linné (Fam. Pedaliaceae) by expression in a hydraulic press or by solvent extraction. The crude oil thus obtained is refined to obtain an oil suitable for food or pharmaceutical use. Improved color and odor may be obtained by further refining.

14 Safety

Sesame oil is mainly used in intramuscular and subcutaneous injections; it should not be administered intravenously. It is also used in topical pharmaceutical formulations and consumed as an edible oil.

Although it is generally regarded as an essentially nontoxic and nonirritant material,(17) there have been rare reports of hypersensitivity to sesame oil, with sesamin suspected as being the primary allergen.(18–21) Anaphylactic reactions to sesame seeds have also been reported. However, it is thought that the allergens in the seeds may be inactivated or destroyed by heating as heat-extracted sesame seed oil or baked sesame seeds do not cause anaphylactic reactions in sesame seed-allergic individuals.(22)

LD_{50} (rabbit, IV): 678 μg/kg(23)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Spillages of sesame oil are slippery and should be covered with an inert absorbent material prior to disposal.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IM and SC injections, oral capsules, emulsions, and tablets, also topical preparations). Included in parenteral (IM injections) and nonparenteral (oral capsules and sprays) medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Almond oil; canola oil; corn oil; cottonseed oil; peanut oil; soybean oil; sunflower oil.

18 Comments

—

19 Specific References

1 British Standards Institute. *Specification for Crude Vegetable Fats, BS 7207*. London: BSI, 1990.
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CG Cable.

22 Date of Revision

23 August 2005.

Shellac

1 Nonproprietary Names

BP: Shellac
JP: Purified shellac, White shellac
PhEur: Lacca
USPNF: Shellac

2 Synonyms

Bleached shellac; *CertiSeal*; dewaxed orange shellac; E904; lac; *Mantrolac R-49*; orange shellac; refined bleached shellac; regular bleached shellac; *Swanlac*.

3 Chemical Name and CAS Registry Number

Shellac [9000-59-3]

4 Empirical Formula and Molecular Weight

Shellac is a naturally occurring material consisting of a complex mixture of constituents that may be obtained in various refined or modified forms; *see* Section 13.

The PhEur 2005 defines four types of shellac depending on the nature of the treatment of the crude shellac (seed lac): wax-containing shellac; bleached shellac; dewaxed shellac; and bleached dewaxed shellac. The USPNF 23 similarly defines four types of shellac: orange shellac; dewaxed orange shellac; regular bleached (white) shellac; and refined bleached shellac. The JP 2001 defines two types: purified shellac and white shellac (bleached).

Elementary analysis reveals that shellac contains carbon, hydrogen, oxygen, and a negligible amount of ash. A formula of $C_{60}H_{90}O_{15}$ and an average molecular weight of 1000 is assigned to shellac. Although its composition has not been fully elucidated, the main component of shellac (about 95%) is a resin that gives a mixture of aliphatic and alicyclic hydroxy acids and polyesters on mild basic hydrolysis. Some of the compounds identified and named include aleuritic, butolic, kerrolic, and shellolic acids. The major component of the aliphatic fraction is aleuritic acid, while the major component of the alicyclic fraction is shellolic acid.

Shellac also contains about 5–6% wax along with gluten, other impurities, and a small amount of pigment. The exact composition of shellac may vary depending upon the country of origin and method of manufacture.(1,2)

5 Structural Formula

See Section 4.

6 Functional Category

Coating agent.

7 Applications in Pharmaceutical Formulation or Technology

Shellac has been used in pharmaceutical formulations for the enteric coating of tablets and beads,(3) the material usually being applied as a 35% w/v alcoholic solution; *see also* Section 18.

It is a primary ingredient of pharmaceutical printing inks for monogramming capsules and tablets, and can be applied as a 40% w/v alcoholic solution. It has also been used to apply one or two sealing coats to tablet cores to protect them from moisture before being film- or sugar-coated.

Shellac may also be used in food products and cosmetics.

8 Description

Shellac is a naturally occurring material that may be obtained in a variety of refined or modified forms; *see* Sections 4 and 13.

Generally, shellac occurs as hard, brittle, transparent, pale lemon-yellow to brownish orange-colored flakes of varying size and shape; it is also available as a powder. Shellac is tasteless and odorless, or may have a faint odor.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for shellac.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	—	+	+
Characters	—	+	—
Heavy metals	⩽10 ppm	⩽10 ppm	⩽0.001%
Arsenic	⩽5 ppm	⩽3 ppm	—
Ethanol-insoluble substances	⩽2.0%	—	—
Rosin	+	—	+
Total ash	⩽1.0%	—	—
Acid value (on dried basis)	60–80	65–95	+
Dewaxed orange shellac	—	—	71–79
Orange shellac	—	—	68–76
Refined bleached shellac	—	—	75–91
Regular bleached shellac	—	—	73–89
Loss on drying	⩽2.0%	+	+
Dewaxed orange shellac	—	—	⩽2.0%
Orange shellac	—	—	⩽2.0%
Refined bleached shellac	—	—	⩽6.0%
Regular bleached shellac	—	⩽6.0%	⩽6.0%
Unbleached shellac	—	⩽2.0%	—
Wax	⩽20 mg	—	+
Dewaxed orange shellac	—	—	⩽0.2%
Orange shellac	—	—	⩽5.5%
Refined bleached shellac	—	—	⩽0.2%
Regular bleached shellac	—	—	⩽5.5%

10 Typical Properties

Alcohol-insoluble matter: ⩽1.0%
Ash: ⩽1.0%
Density: 1.035–1.140 g/cm^3
Hydroxyl value: 230–280
Iodine number: 10–18
Melting point: 115–120°C

Refractive index: n_D^{20} = 1.5210–1.5272
Saponification value: 185–210
Solubility: *see* Table II.

Table II: Solubility of shellac.

Solvent	Solubility at 20°C
Alkalis	Soluble
Aqueous ethanolamine solution	Soluble
Benzene	1 in 10
Ethanol	1 in 2
Ethanol (95%)	1 in 1.2 (very slowly soluble)
Ether	1 in 8
Hexane	Practically insoluble
Propylene glycol	1 in 10
Water	Practically insoluble

11 Stability and Storage Conditions

After long periods of storage, shellac becomes less readily soluble in alcohol, less fluid on heating, and darker in color. Shellac-coated tablets may have increased disintegration times following prolonged storage owing to changes in the physical characteristics of the coating; *see* Section 18.(4)

Shellac should be stored in a well-closed container at temperatures below 27°C. Wax-containing grades should be mixed before use to ensure uniform distribution of the wax.

12 Incompatibilities

Shellac is chemically reactive with aqueous alkalis, organic bases, alcohols, and agents that esterify hydroxyl groups. Therefore, shellac should be used with caution in the presence of such compounds.

13 Method of Manufacture

Shellac or lac is obtained by purification of the resinous secretion of the insect *Laccifero* (*Tachardia*) *lacca Kerr* (Homoptera, Coccidae). The insect lives on the sap of the stems of various trees; secretions are found most abundantly on the smaller branches and twigs, which are broken off and constitute sticklac. After scraping of the twigs and soaking in water, the water-soluble components are removed by treatment with dilute alkali. The resulting water-insoluble material is called seed lac.

Historically, seed lac was processed into shellac by melting the seed lac in a muslin bag suspended over a fire. Shellac could then be squeezed from the bag by hand and poured into molds to produce button shellac. Alternatively, the molten shellac was collected and allowed to cool as discs or wafer-thin sheets.

Today, most shellac is produced on a commercial scale using machine processes involving extraction from seed lac using steam heat or solvent extraction with hot ethanol. Shellac produced by the heat and solvent extraction processes cannot usually be differentiated by chemical tests.

Various different grades of modified or refined shellac are available, which may be broadly defined as either bleached or orange shellac. Orange shellac is essentially the crude shellac obtained from seed lac, as described above. It may retain most of its wax or be dewaxed, and may contain less of the natural color than was originally present. The quantities of wax, coloring material, and other impurities present may vary; the physical properties of orange shellac may therefore also vary depending upon its source or the processing methods used.

Bleached or white shellac is obtained by dissolving shellac in aqueous sodium carbonate, bleaching the solution with sodium hypochlorite, and precipitating the bleached shellac with 2 N sulfuric acid. Removal of wax by filtration results in a refined bleached shellac.

Most commercial shellac is produced in India and Thailand; smaller amounts come from Burma and Malaysia.

14 Safety

Shellac is used in oral pharmaceutical formulations, food products, and cosmetics. It is generally regarded as an essentially nonirritant and nontoxic material at the levels employed as an excipient. However, excessive consumption of shellac may be harmful.

15 Handling Precautions

Shellac may be harmful if ingested in large quantities. It is irritating to the eyes, and to the respiratory system if inhaled as dust. Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust respirator are recommended. Shellac should be handled in a well-ventilated environment.

16 Regulatory Status

Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Aleuritic acid; pharmaceutical glaze; polyvinyl acetate phthalate; shellolic acid.

Aleuritic acid

Empirical formula: $C_{16}H_{32}O_5$
Molecular weight: 304.42
CAS number: [533-87-9]
Synonyms: DL-*erythro*-9,10,16,-trihydroxyhexadecanoic acid; 9,10,16-trihydroxypalmitic acid; 8,9,15-trihydroxypentadecane-1-carboxylic acid.
Melting point: 100–101°C
Solubility: soluble in methanol.
Comments: component of shellac. The EINECS number for aleuritic acid is 208-578-8.

Pharmaceutical glaze

Comments: pharmaceutical glaze is a specially denatured alcoholic solution of shellac containing between 20% and 57% of anhydrous shellac. It may be prepared using either ethanol or ethanol 95% and may contain waxes and titanium dioxide as an opacifing agent.

Shellolic acid

Empirical formula: $C_{15}H_{20}O_6$
Molecular weight: 296.33
CAS number: [4448-95-7]
Synonyms: 10β,13-dihydroxycedr-8-ene-12,15-dioic acid; 2,3,4,7,8,8α-hexahydro-4-hydroxy-8-(hydroxymethyl)-8-methyl-1*H*-3α,7-methanoazulene-3,6-dicarboxylic acid.
Melting point: 204–207°C
Comments: component of shellac.

18 Comments

Shellac is insoluble in acidic conditions but is soluble at higher pH; it therefore appears to be a suitable enteric-coating material. However, in practice, delayed disintegration and drug release may occur *in vivo* as shellac is insoluble in the slightly acidic environment of the upper intestine. Additives such as lauric acid may be added to plasticize and improve disintegration of shellac films, although shellac tends not to be used in new drug formulations as an enteric-coating agent.

Studies using the USP disintegration test for enteric-coated tablets have indicated that there is a marked increase in the disintegration time over a 6-month storage period for shellac-coated tablets.(4) It is likely that this effect is due to the polymerization of shellac, which occurs over storage periods of this duration. A specification for shellac is contained in the Food Chemicals Codex (FCC).

The EINECS number for shellac is 232-549-9.

19 Specific References

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21 Authors

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22 Date of Revision

18 August 2005.

Simethicone

1 Nonproprietary Names

BP: Simeticone
PhEur: Simeticonum
USP: Simethicone

2 Synonyms

Dow Corning Q7-2243 LVA; *Dow Corning Q7-2587*; polydimethylsiloxane–silicon dioxide mixture; *Sentry Simethicone*; simeticone.

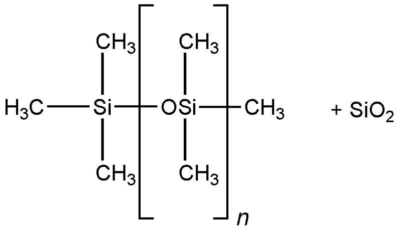
3 Chemical Name and CAS Registry Number

α-(Trimethysilyl-ω-methylpoly[oxy(dimethylsilylene)], mixture with silicon dioxide [8050-81-5]

4 Empirical Formula and Molecular Weight

See Section 8.

5 Structural Formula



$$H_3C-Si(CH_3)_2-[-OSi(CH_3)_2-]_n-CH_3 + SiO_2$$

where $n = 200–350$

6 Functional Category

Antifoaming agent; tablet diluent; water-repelling agent.

7 Applications in Pharmaceutical Formulation or Technology

The main use of simethicone as an excipient is as an antifoaming agent in pharmaceutical manufacturing processes, for which 1–50 ppm is used.

Therapeutically, simethicone is included in a number of oral pharmaceutical formulations as an antiflatulent, although its therapeutic benefit is questionable.(1) It is also included in antacid products such as tablets or capsules.(2–6) In some types of surgical or gastroscopic procedures where gas is used to inflate the body cavity, a defoaming preparation containing simethicone may be used in the area to control foaming of the fluids.

When simethicone is used in aqueous formulations, it should be emulsified to ensure compatibility with the aqueous system and components.

In the USA, up to 10 ppm of simethicone may be used in food products.

8 Description

The PhEur 2005 and USP 28 describe simethicone as a mixture of fully methylated linear siloxane polymers containing repeating units of the formula $[-(CH_3)_2SiO-]_n$, stabilized with trimethylsiloxy end-blocking units of the formula $[(CH_3)_3 SiO-]$, and silicon dioxide. It contains not less than 90.5% and not more than 99.0% of the polydimethylsiloxane $[-(CH_3)_2SiO-]_n$, and not less than 4.0% and not more than 7.0% of silicon dioxide. The PhEur 2005 additionally states that the degree of polymerization is between 20–400.

Simethicone occurs as a translucent, gray-colored, viscous fluid. It has a molecular weight of 14 000–21 000.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for simethicone.

Test	PhEur 2005	USP 28
Identification	+	+
Characters	+	—
Acidity	+	—
Defoaming activity	⩽15 seconds	⩽15 seconds
Loss on heating	—	⩽18%
Volatile matter	⩽1.0%	—
Heavy metals	⩽5 ppm	⩽5 μg/g
Organic volatile impurities	—	+
Mineral oils	+	—
Phenylated compounds	+	—
Assay (dimethicone)	+	—
Assay (silicon dioxide)	—	4.0–7.0%
Assay (silica)	⩽7.0%	—
Assay (polydimethylsiloxane)	90.5–99.0%	90.5–99.0%

10 Typical Properties

Boiling point: 35°C

Refractive index: $n_D^{20} = 0.965–0.970$

Solubility: practically insoluble in ethanol (95%) and water. The liquid phase is soluble in benzene, chloroform, and ether, but silicon dioxide remains as a residue in these solvents.

Specific gravity: 0.95–0.98 at 25°C

Viscosity (kinematic): 370 mm^2/s at 25°C for *Dow Corning Q7-2243 LVA*.

11 Stability and Storage Conditions

Simethicone is generally regarded as a stable material when stored in the original unopened container. A shelf-life of 18 months from the date of manufacture is typical. However, some simethicone products have a tendency for the silicon dioxide to settle slightly and containers of simethicone should therefore be shaken thoroughly to ensure uniformity of contents before sampling or use. Simethicone should be stored in a cool, dry, location away from oxidizing materials.

Simethicone can be sterilized by dry heating or autoclaving. With dry heating, a minimum of 4 hours at 160°C is required.

12 Incompatibilities

Simethicone as supplied is not generally compatible with aqueous systems and will float like an oil on a formulation unless it is first emulsified. It should not be used in formulations or processing conditions that are very acidic (below pH 3) or highly alkaline (above pH 10), since these conditions may have some tendency to break the polydimethylsiloxane polymer. Simethicone cannot normally be mixed with polar solvents of any kind because it is very minimally soluble. Simethicone is incompatible with oxidizing agents.

13 Method of Manufacture

Silicon dioxide is initially rendered hydrophobic in one of a variety of proprietary processes specific to a particular manufacturer. It is then slowly mixed with the silicone fluids in a formulation. After mixing, the simethicone is milled to ensure uniformity.

14 Safety

Simethicone is used in cosmetics, foods, and oral and topical pharmaceutical formulations and is generally regarded as a relatively nontoxic and nonirritant material when used as an excipient. Direct contact with the eye may cause irritation.

Therapeutically, oral doses of 125–250 mg of simethicone, three or four times daily, have been given as an antiflatulent. Doses of 20–40 mg of simethicone have been given with feeds to relieve colic in infants.(7)

LD_{50} (dog, IV): 0.9 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Simethicone should be handled in areas with adequate ventilation.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral emulsions, powders, solutions, suspensions, tablets, and rectal and topical preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Cyclomethicone; dimethicone.

18 Comments

—

19 Specific References

1 Anonymous. Simethicone for gastrointestinal gas. *Med Lett Drugs Ther* 1996; **38**: 57–58.
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21 Authors

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22 Date of Revision

22 August 2005.

Sodium Acetate

1 Nonproprietary Names

BP: Sodium acetate
JP: Sodium acetate
PhEur: Natrii acetas trihydricus
USP: Sodium acetate

2 Synonyms

Acetic acid, sodium salt; E262; sodium ethanoate.

3 Chemical Name and CAS Registry Number

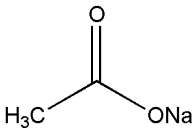
Sodium acetate anhydrous [127-09-3]
Sodium acetate trihydrate [6131-90-4]

4 Empirical Formula and Molecular Weight

$C_2H_3NaO_2$	82.0 (for anhydrous)
$C_2H_3NaO_2{\cdot}3H_2O$	136.1 (for trihydrate)

Note that the trihydrate is the material described in the JP2001, PhEur 2005 and USP 28, although the PhEur 2005 is the only pharmacopeia that makes this explicit with the title of the monograph.

5 Structural Formula



6 Functional Category

Antimicrobial preservative; buffering agent; flavoring agent, stabilizing agent.

7 Applications in Pharmaceutical Formulation or Technology

Sodium acetate is used as a buffering agent in various intramuscular, intravenous, topical, ophthalmic, nasal, oral, otic, and subcutaneous formulations. It may be used to reduce the bitterness of oral pharmaceuticals.(1) It can be used to enhance the antimicrobial properties of formulations; it has been shown to inhibit the growth of *S. aureus* and *E. coli*, but not *C. albicans* in protein hydrolysate solutions.(2) It is widely used in the food industry as a preservative.(3) Sodium acetate has also been used therapeutically for the treatment of metabolic acidosis in premature infants,(4,5) and in hemodialysis solutions.(6,7)

8 Description

Sodium acetate occurs as colorless, transparent crystals or a granular crystalline powder with a slight acetic acid odor.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium acetate.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Description	+	—	—
Characters	—	+	—
Appearance of solution	+	+	—
Acid or alkali	+	—	—
pH	—	7.5–9.0	7.5–9.2
Insoluble matter	—	—	⩽0.05%
Chloride	⩽0.011%	⩽200 ppm	⩽0.035%
Sulfate	⩽0.017%	⩽200 ppm	⩽0.005%
Heavy metals	⩽10 ppm	⩽10 ppm	⩽0.001%
Calcium and magnesium	+	⩽50 ppm	+
Potassium	—	—	+
Arsenic	⩽2 ppm	⩽2 ppm	—
Iron	—	⩽10 ppm	—
Reducing substances	+	+	—
Aluminum	—	⩽0.2 ppm	⩽0.2 μg/g
Loss on drying			
anhydrous	—	—	⩽1.0%
trihydrate	39.0–40.5%	39.0–40.5%	38.0–41.0%
Organic volatile impurities	—	—	+
Assay (dried basis)	⩾99.5%	99.0–101.0%	99.0–101.0%

10 Typical Properties

Acidity/alkalinity: pH = 7.5–9.0 (5% w/v aqueous solution)
Hygroscopicity: the anhydrous and trihydrate sodium acetate are hygroscopic.
Solubility: soluble 1 in 0.8 in water, 1 in 20 in ethanol (95%).
Melting point: 58°C for trihydrate; 324°C for anhydrous.(8)
Specific gravity: 1.53

11 Stability and Storage Conditions

Sodium acetate should be stored in airtight containers.

12 Incompatibilities

Sodium acetate reacts with acidic and basic components. It will react violently with fluorine, potassium nitrate, and diketene.

13 Method of Manufacture

Sodium acetate is prepared by neutralization of acetic acid with sodium carbonate.

14 Safety

Sodium acetate is widely used in cosmetics, foods, and pharmaceutical formulations (*see* Section 18), and is generally regarded as a nontoxic and nonirritant material.

A short-term feeding study in chickens with a diet supplemented with 5.44% sodium acetate showed reduced growth rates that were attributed to the sodium content.(9) Sodium acetate is poisonous if injected intravenously, is moderately toxic by ingestion, and is an irritant to the skin and eyes.(10)

LD_{50} (rat, oral): 3.53 g/kg(10)
LD_{50} (mouse, IV): 0.38 g/kg(11)
LD_{50} (mouse, SC): 8.0 g/kg(10)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium acetate is a mild skin and eye irritant; gloves and eye protection are recommended. On exposure, wash eyes and skin with large amounts of water. Inhalation of dust may cause pulmonary tract problems. When heated to decomposition, sodium acetate emits toxic fumes of NaO_2.(10)

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (injections, nasal, otic, ophthalmic, and oral preparations).

17 Related Substances

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18 Comments

Sodium acetate was shown to enhance aqueous humor to plasma concentration ratio of timolol by about 20-fold in an ophthalmic monoisopropyl PVM-MA matrix system, presumably by decreasing systemic absorption.(12)

Sodium acetate has also been used experimentally in matrix tablet formulations, where it increased the effect of carbomer as a sustained release matrix.(13)

A specification for sodium acetate is contained within the Food Chemicals Codex (FCC). The PhEur 2005 also contains a monograph on sodium acetate [1-^{11}C] injection under Radiopharmaceutical Preparations.

The EINECS number for sodium acetate is 204-823-8.

19 Specific References

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20 General References

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21 Authors

WG Chambliss.

22 Date of Revision

8 August 2005.

Sodium Alginate

1 Nonproprietary Names

BP: Sodium alginate
PhEur: Natrii alginas
USPNF: Sodium alginate

2 Synonyms

Algin; alginic acid, sodium salt; E401; *Kelcosol*; *Keltone*; *Protanal*; sodium polymannuronate.

3 Chemical Name and CAS Registry Number

Sodium alginate [9005-38-3]

4 Empirical Formula and Molecular Weight

Sodium alginate consists chiefly of the sodium salt of alginic acid, which is a mixture of polyuronic acids composed of residues of D-mannuronic acid and L-guluronic acid.

The block structure and molecular weight of sodium alginate samples has been investigated.(1)

5 Structural Formula

See Section 4.

6 Functional Category

Stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Sodium alginate is used in a variety of oral and topical pharmaceutical formulations.(2) In tablet formulations, sodium alginate may be used as both a binder and disintegrant;(3) it has been used as a diluent in capsule formulations.(4) Sodium alginate has also been used in the preparation of sustained-release oral formulations since it can delay the dissolution of a drug from tablets,(5–7) capsules,(8) and aqueous suspensions.(9)

In topical formulations, sodium alginate is widely used as a thickening and suspending agent in a variety of pastes, creams, and gels, and as a stabilizing agent for oil-in-water emulsions.

Recently, sodium alginate has been used for the aqueous microencapsulation of drugs,(10) in contrast with the more conventional microencapsulation techniques which use organic-solvent systems. It has also been used in the formation of nanoparticles.(11)

The adhesiveness of hydrogels prepared from sodium alginate has been investigated(12) and drug release from oral mucosal adhesive tablets,(13) and buccal gels,(14,15) based on sodium alginate have been reported. Other novel delivery systems containing sodium alginate include ophthalmic solutions that form a gel *in situ* when administered to the eye;(16,17) an *in situ* forming gel containing paracetamol for oral administration;(18) and a freeze-dried device intended for the delivery of bone-growth factors.(19)

Hydrogel systems containing alginates have also been investigated for delivery of proteins and peptides.(20)

Therapeutically, sodium alginate has been used in combination with an H_2-receptor antagonist in the management of gastroesophageal reflux,(21) and as a hemostatic agent in surgical dressings.(22,23) Alginate dressings, used to treat exuding wounds, often contain significant amounts of sodium alginate as this improves the gelling properties.(24) Sponges composed of sodium alginate and chitosan produce a sustained drug release and may be useful as wound dressings or as tissue engineering matrices.(25)

Sodium alginate is also used in cosmetics and food products; *see* Table I.

Table I: Uses of sodium alginate.

Use	Concentration (%)
Pastes and creams	5–10
Stabilizer in emulsions	1–3
Suspending agent	1–5
Tablet binder	1–3
Tablet disintegrant	2.5–10

8 Description

Sodium alginate occurs as an odorless and tasteless, white to pale yellowish-brown colored powder.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for sodium alginate.

Test	PhEur 2005	USPNF 23
Characters	+	+
Identification	+	+
Appearance of solution	+	—
Microbial limits	⩽1000/g	⩽200/g
Loss on drying	⩽15.0%	⩽15.0%
Ash	—	18.0–27.0%
Sulfated ash	30.0–36.0%	—
Arsenic	—	⩽1.5 ppm
Calcium	⩽1.5%	—
Chlorides	⩽1.0%	—
Lead	—	⩽0.001%
Heavy metals	⩽20 ppm	⩽0.004%
Assay (dried basis)	—	90.8–106.0%

10 Typical Properties

Acidity/alkalinity: pH ≈7.2 for a 1% w/v aqueous solution.

Solubility: practically insoluble in ethanol (95%), ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30%. Also, practically insoluble in other organic solvents and aqueous acidic solutions in which the pH is less than 3. Slowly soluble in water, forming a viscous colloidal solution.

Viscosity (dynamic): various grades of sodium alginate are commercially available that yield aqueous solutions of varying viscosity. Typically, a 1% w/v aqueous solution, at 20°C, will have a viscosity of 20–400 mPa s (20–400 cP). Viscosity may vary depending upon concentration, pH, temperature, or the presence of metal ions.(26–28) Above pH 10, viscosity decreases, *see also* Alginic Acid and Section 11.

11 Stability and Storage Conditions

Sodium alginate is a hygroscopic material, although it is stable if stored at low relative humidities and a cool temperature.

Aqueous solutions of sodium alginate are most stable at pH 4–10. Below pH 3, alginic acid is precipitated. A 1% w/v aqueous solution of sodium alginate exposed to differing temperatures had a viscosity 60–80% of its original value after storage for 2 years.(29) Solutions should not be stored in metal containers.

Sodium alginate solutions are susceptible on storage to microbial spoilage, which may affect solution viscosity. Solutions are ideally sterilized using ethylene oxide, although filtration using a 0.45 μm filter also has only a slight adverse effect on solution viscosity.(30) Heating sodium alginate solutions to temperatures above 70°C causes depolymerization with a subsequent loss of viscosity. Autoclaving of solutions can cause a decrease in viscosity, which may vary depending upon the nature of any other substances present.(30,31) Gamma irradiation should not be used to sterilize sodium alginate solutions since this process severely reduces solution viscosity.(30,32)

Preparations for external use may be preserved by the addition of 0.1% chlorocresol, 0.1% chloroxylenol, or parabens. If the medium is acidic, benzoic acid may also be used.

The bulk material should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Sodium alginate is incompatible with acridine derivatives, crystal violet, phenylmercuric acetate and nitrate, calcium salts, heavy metals, and ethanol in concentrations greater than 5%. Low concentrations of electrolytes cause an increase in viscosity but high electrolyte concentrations cause salting-out of sodium alginate; salting-out occurs if more than 4% of sodium chloride is present.

13 Method of Manufacture

Alginic acid is extracted from brown seaweed and is neutralized with sodium bicarbonate to form sodium alginate.

14 Safety

Sodium alginate is widely used in cosmetics, food products, and pharmaceutical formulations, such as tablets and topical products, including wound dressings. It is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may be harmful. A study in five healthy male volunteers fed a daily intake of 175 mg/kg body-weight of sodium alginate for 7 days, followed by a daily intake of 200 mg/kg body-weight of sodium alginate for a further 16 days, showed no significant adverse effects.(33)

The WHO has not specified an acceptable daily intake for alginic acid and alginate salts as the levels used in food do not represent a hazard to health.(34)

Inhalation of alginate dust may be irritant and has been associated with industrial-related asthma in workers involved in alginate production. However, it appears that the cases of asthma were linked to exposure to seaweed dust rather than pure alginate dust.(35)

LD_{50} (cat, IP): 0.25 g/kg(36)
LD_{50} (mouse, IV): 0.2 g/kg
LD_{50} (rabbit, IV): 0.1 g/kg
LD_{50} (rat, IV): 1 g/kg
LD_{50} (rat, oral): >5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium alginate may be irritant to the eyes or respiratory system if inhaled as dust; *see* Section 14. Eye protection, gloves, and a dust respirator are recommended. Sodium alginate should be handled in a well-ventilated environment.

16 Regulatory Status

GRAS listed. Accepted in Europe for use as a food additive. Included in the FDA Inactive Ingredients Guide (oral suspensions and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Alginic acid; calcium alginate; potassium alginate; propylene glycol alginate.

18 Comments

A number of different grades of sodium alginate, which have different solution viscosities, are commercially available. Many different alginate salts and derivatives are also commercially available including ammonium alginate; calcium alginate; magnesium alginate, and potassium alginate.

To assist in the preparation of dispersions of sodium alginate, the material may be mixed with a dispersing agent such as sucrose, ethanol, glycerol, or propylene glycol. A specification for sodium alginate is contained in the Food Chemicals Codex (FCC).

See also Alginic Acid for further information.

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21 Authors

CG Cable.

22 Date of Revision

20 August 2005.

Sodium Ascorbate

1 Nonproprietary Names

PhEur: Natrii ascorbas
USP: Sodium ascorbate

2 Synonyms

L-Ascorbic acid monosodium salt; E301; 3-oxo-L-gulofuranolactone sodium enolate; *SA-99*; vitamin C sodium.

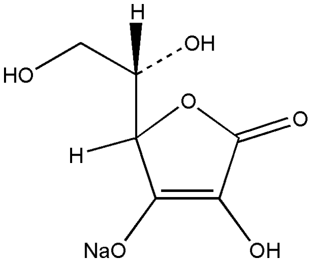
3 Chemical Name and CAS Registry Number

Monosodium L-(+)-ascorbate [134-03-2]

4 Empirical Formula and Molecular Weight

$C_6H_7NaO_6$ 198.11

5 Structural Formula



6 Functional Category

Antioxidant; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

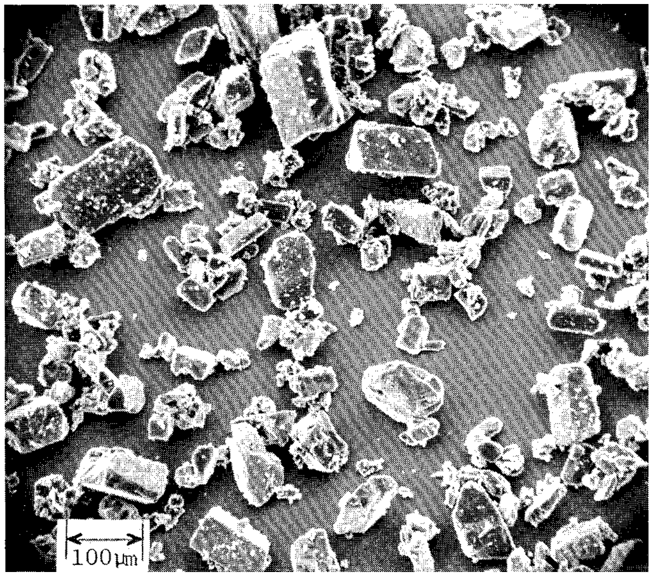
Sodium ascorbate is used as an antioxidant in pharmaceutical formulations, and also in food products where it increases the effectiveness of sodium nitrite against growth of *Listeria monocytogenes* in cooked meats. It improves gel cohesiveness and sensory firmness of fiberized products regardless of vacuum treatment.

It is also used therapeutically as a source of vitamin C in tablets and parenteral preparations.

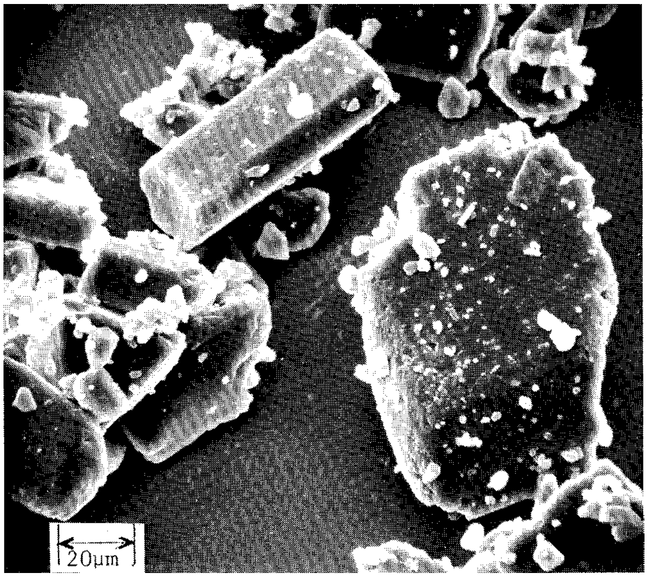
8 Description

Sodium ascorbate occurs as a white or slightly yellow-colored, practically odorless, crystalline powder with a pleasant saline taste.

SEM: 1
Excipient: Sodium ascorbate USP
Manufacturer: Pfizer Ltd.
Lot No: 9B-1 (C92220-C4025)
Magnification: 120×
Voltage: 20 kV



SEM: 2
Excipient: Sodium ascorbate USP
Manufacturer: Pfizer Ltd.
Lot No: 9B-1 (C92220-C4025)
Magnification: 600×
Voltage: 20 kV



9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium ascorbate.

Test	PhEur 2005	USP 28
Identification	+	+
Characters	+	—
Appearance of solution	+	—
pH	7.0–8.0	7.0–8.0
Specific optical rotation (10% w/v aqueous solution)	+103° to +108°	+103° to +108°
Oxalic acid	⩽0.30%	—
Benzene	⩽2 ppm	—
Sulfates	⩽150 ppm	—
Copper	⩽5 ppm	—
Iron	⩽2 ppm	—
Nickel	⩽1 ppm	—
Heavy metals	⩽10 ppm	⩽0.002%
Loss on drying	⩽0.25%	⩽0.25%
Organic volatile impurities	—	+
Assay (dried basis)	99.0–101.0%	99.0–101.0%

10 Typical Properties

Acidity/alkalinity: pH = 7–8 (10% w/v aqueous solution)

Density (tapped):
0.6–1.1 g/cm^3 for fine powder;
0.8–1.1 g/cm^3 for fine granular grade.

Density (true): 1.826 g/cm^3

Hygroscopicity: not hygroscopic. Sodium ascorbate adsorbs practically no water up to 80% relative humidity at 20°C and less than 1% w/w of water at 90% relative humidity.

Melting point: 218°C (with decomposition)

Particle size distribution: various grades of sodium ascorbate with different particle-size distributions are commercially available, e.g., approximately 98% passes through a 149 μm mesh for a fine powder grade (Takeda), and approximately 95% passes through a 840 μm mesh for a standard grade (Takeda).

Solubility: *see* Table II.

Table II: Solubility of sodium ascorbate.

Solvent	Solubility at 20°C unless otherwise stated
Chloroform	Practically insoluble
Ethanol (95%)	Very slightly soluble
Ether	Practically insoluble
Water	1 in 1.6 1 in 1.3 at 75°C

Specific gravity:
1.782 for powder at 20°C;
1.005 for 1% w/v aqueous solution at 25°C;
1.026 for 5% w/v aqueous solution at 25°C.

Specific rotation $[\alpha]_D^{20}$: +104.4°(10% w/v aqueous solution)

11 Stability and Storage Conditions

Sodium ascorbate is relatively stable in air, although it gradually darkens on exposure to light. Aqueous solutions are unstable and subject to rapid oxidation in air at pH > 6.0.

The bulk material should be stored in a well-closed nonmetallic container, protected from light, in a cool, dry place.

12 Incompatibilities

Incompatible with oxidizing agents, heavy metal ions, especially copper and iron, methenamine, sodium nitrite, sodium salicylate, and theobromine salicylate. The aqueous solution is reported to be incompatible with stainless steel filters.(1)

13 Method of Manufacture

An equivalent amount of sodium bicarbonate is added to a solution of ascorbic acid in water. Following the cessation of effervescence, the addition of propan-2-ol precipitates sodium ascorbate.

14 Safety

The parenteral administration of 0.25–1.00 g of sodium ascorbate, given daily in divided doses, is recommended in the treatment of vitamin C deficiencies. Various adverse reactions have been reported following the administration of 1 g or more of sodium ascorbate, although ascorbic acid and sodium ascorbate are usually well tolerated; *see* Ascorbic acid. There have been no reports of adverse effects associated with the much lower concentrations of sodium ascorbate and ascorbic acid, which are employed as antioxidants.

The WHO has set an acceptable daily intake of ascorbic acid, potassium ascorbate, and sodium ascorbate, as antioxidants in food, at up to 15 mg/kg body-weight in addition to that naturally present in food.(2)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium ascorbate may be irritant to the eyes. Eye protection and rubber or plastic gloves are recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IV preparations; oral tablets). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Ascorbic acid; ascorbyl palmitate; calcium ascorbate.

Calcium ascorbate

Empirical formula: $C_{12}H_{14}O_{12}Ca$
Molecular weight: 390.31
CAS number: [5743-27-1]
Synonyms: calcium L-(+)-ascorbate; *CCal-97*; E302.

18 Comments

1 mg of sodium ascorbate is equivalent to 0.8890 mg of ascorbic acid (1 mg of ascorbic acid is equivalent to 1.1248 mg of sodium ascorbate); 1 g of sodium ascorbate contains approximately 5 mmol of sodium. A specification for sodium ascorbate is contained in the Food Chemicals Codex (FCC).

The EINECS number for sodium ascorbate is 205-126-1.

19 Specific References

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21 Authors

CP McCoy.

22 Date of Revision

17 August 2005.

Sodium Benzoate

1 Nonproprietary Names

BP: Sodium benzoate
JP: Sodium benzoate
PhEur: Natrii benzoas
USPNF : Sodium benzoate

2 Synonyms

Benzoic acid sodium salt; benzoate of soda; E211; natrium benzoicum; sobenate; sodii benzoas; sodium benzoic acid.

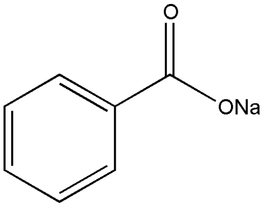
3 Chemical Name and CAS Registry Number

Sodium benzoate [532-32-1]

4 Empirical Formula and Molecular Weight

$C_7H_5NaO_2$ 144.11

5 Structural Formula



6 Functional Category

Antimicrobial preservative; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

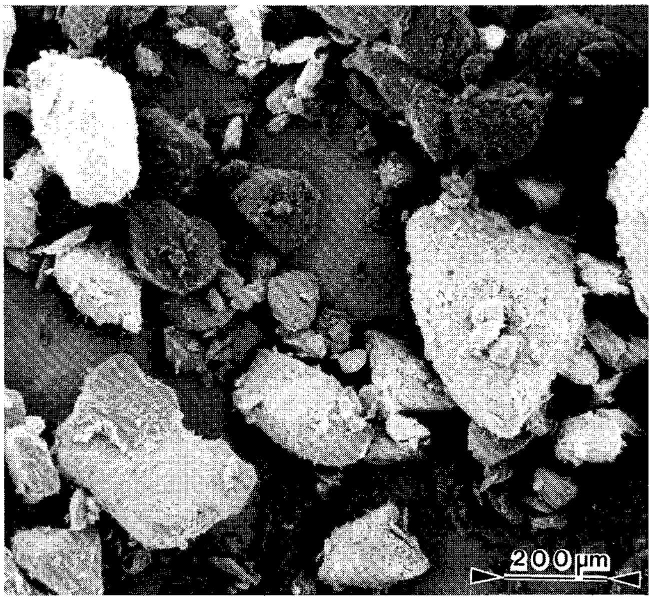
Sodium benzoate is used primarily as an antimicrobial preservative in cosmetics, foods, and pharmaceuticals. It is used in concentrations of 0.02–0.5% in oral medicines, 0.5% in parenteral products, and 0.1–0.5% in cosmetics. The usefulness of sodium benzoate as a preservative is limited by its effectiveness over a narrow pH range; *see* Section 10.

Sodium benzoate is used in preference to benzoic acid in some circumstances, owing to its greater solubility. However, in some applications it may impart an unpleasant flavor to a product. Sodium benzoate has also been used as a tablet lubricant(1) at 2–5% w/w concentrations. Solutions of sodium benzoate have also been administered, orally or intravenously, in order to determine liver function.

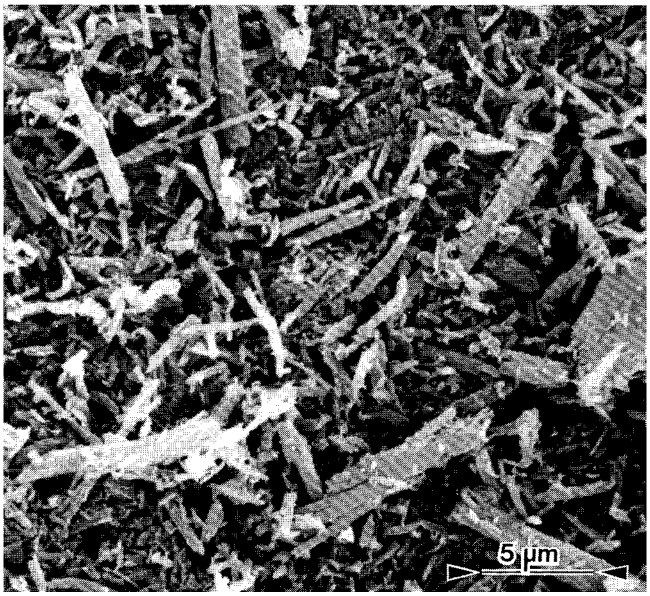
8 Description

Sodium benzoate occurs as a white granular or crystalline, slightly hygroscopic powder. It is odorless, or with faint odor of benzoin and has an unpleasant sweet and saline taste.

SEM: 1
Excipient: Sodium benzoate
Manufacturer: Bush Boake Allen Corp.
Magnification: 60×



SEM: 2
Excipient: Sodium benzoate
Manufacturer: Bush Boake Allen Corp.
Magnification: 2400×



9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium benzoate.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	+	+	—
Acidity or alkalinity	+	+	+
Appearance of solution	+	+	—
Arsenic	⩽2 ppm	—	—
Chloride	+	⩽200 ppm	—
Heavy metals	⩽20 ppm	⩽10 ppm	⩽0.001%
Organic volatile impurities	—	—	+
Loss on drying	⩽1.5%	⩽2.0%	⩽1.5%
Phthalic acid	+	—	—
Sulfate	⩽0.120%	—	—
Total chlorine	—	⩽300 ppm	—
Assay (dried basis)	⩾99.0%	99.0–100.5%	99.0–100.5%

10 Typical Properties

Acidity/alkalinity: pH = 8.0 (saturated aqueous solution at 25°C). It is relatively inactive above approximately pH 5.

Antimicrobial activity: sodium benzoate has both bacteriostatic and antifungal properties attributed to undissociated benzoic acid, hence preservative efficacy is best seen in acidic solutions (pH 2–5). In alkaline conditions it is almost without effect.

Density: 1.497–1.527 g/cm^3 at 24°C

Freezing point depression: 0.24°C (1.0% w/v)

Osmolarity: a 2.25% w/v aqueous solution is iso-osmotic with serum.

Partition coefficients:

Vegetable oil : water = 3–6

Solubility: *see* Table II.

Table II: Solubility for sodium benzoate.

Solvent	Solubility at 20°C unless otherwise stated
Ethanol (95%)	1 in 75
Ethanol (90%)	1 in 50
Water	1 in 1.8 1 in 1.4 at 100°C

11 Stability and Storage Conditions

Aqueous solutions may be sterilized by autoclaving or filtration.

The bulk material should be stored in a well-closed container, in a cool, dry place.

12 Incompatibilities

Incompatible with quaternary compounds, gelatin, ferric salts, calcium salts, and salts of heavy metals, including silver, lead, and mercury. Preservative activity may be reduced by interactions with kaolin(2) or nonionic surfactants.

13 Method of Manufacture

Prepared by the treatment of benzoic acid with either sodium carbonate or sodium bicarbonate.

14 Safety

Ingested sodium benzoate is conjugated with glycine in the liver to yield hippuric acid, which is excreted in the urine. Symptoms of systemic benzoate toxicity resemble those of salicylates.(3) Whereas oral administration of the free-acid form may cause severe gastric irritation, benzoate salts are well tolerated in large quantities: e.g. 6 g of sodium benzoate in 200 mL of water is administered orally as a liver function test.

Clinical data have indicated that sodium benzoate can produce nonimmunological contact uricartia and nonimmunological immediate contact reactions.(4) However, it is also recognized that these reactions are strictly cutaneous, and can therefore be used safely at concentrations up to 5%. However, this nonimmunological phenomenon should be considered when designing formulations for infants and children.

Other adverse effects include anaphylaxis(5–7) and urticarial reactions, although a controlled study has shown that the incidence of urticaria in patients given benzoic acid is no greater than that with a lactose placebo.(8)

It has been recommended that caffeine and sodium benzoate injection should not be used in neonates;(9) however, sodium benzoate has been used by others in the treatment of some neonatal metabolic disorders.(10) It has been suggested that there is a general adverse effect of benzoate preservatives on the behavior of 3-year-old children, which is detectable by parents, but not by a simple clinical assessment.(11)

The WHO acceptable daily intake of total benzoates, calculated as benzoic acid, has been estimated at up to 5 mg/kg of body-weight.(12,13)

LD_{50} (mouse, IM): 2.3 g/kg(13,14)
LD_{50} (mouse, IV): 1.4 g/kg
LD_{50} (mouse, oral): 1.6 g/kg
LD_{50} (rabbit, oral): 2.0 g/kg
LD_{50} (rat, IV): 1.7 mg/kg
LD_{50} (rat, oral): 4.1 g/kg
See also Benzoic Acid.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium benzoate may be irritant to the eyes and skin. Eye protection and rubber or plastic gloves are recommended.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (dental preparations; IM and IV injections; oral capsules, solutions and tablets; rectal; and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Benzoic acid; potassium benzoate.

18 Comments

Sodium benzoate has been used as an antimicrobial agent used in polymeric films in food packaging.(15) A specification for sodium benzoate is contained in the Food Chemicals Codex (FCC). The EINECS number for sodium benzoate is 208-534-8.

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SC Owen.

22 Date of Revision

16 August 2005.

Sodium Bicarbonate

1 Nonproprietary Names

BP: Sodium bicarbonate
JP: Sodium bicarbonate
PhEur: Natrii hydrogenocarbonas
USP: Sodium bicarbonate

2 Synonyms

Baking soda; E500; *Effer-Soda*; monosodium carbonate; Sal de Vichy; sodium acid carbonate; sodium hydrogen carbonate.

3 Chemical Name and CAS Registry Number

Carbonic acid monosodium salt [144-55-8]

4 Empirical Formula and Molecular Weight

$NaHCO_3$ 84.01

5 Structural Formula

$NaHCO_3$

6 Functional Category

Alkalizing agent; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH in a preparation.

In effervescent tablets and granules, sodium bicarbonate is usually formulated with citric and/or tartaric acid;(1) combinations of citric and tartaric acid are often preferred in formulations as citric acid alone produces a sticky mixture that is difficult to granulate, while if tartaric acid is used alone, granules lose firmness. When the tablets or granules come into contact with water, a chemical reaction occurs, carbon dioxide is evolved, and the product disintegrates.(2,3) Melt granulation in a fluidized bed dryer has been suggested as a one-step method for the manufacture of effervescent granules composed of anhydrous citric acid and sodium bicarbonate, for subsequent compression into tablets.(4)

Tablets may also be prepared with sodium bicarbonate alone since the acid of gastric fluid is sufficient to cause effervescence and disintegration. Sodium bicarbonate is also used in tablet formulations to buffer drug molecules that are weak acids, thereby increasing the rate of tablet dissolution and reducing gastric irritation.(5–7)

The effects of tablet binders, such as polyethylene glycols, microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, and povidone, on the physical and mechanical properties of sodium bicarbonate tablets have also been investigated.(8,9)

Additionally, sodium bicarbonate is used in solutions as a buffering agent for erythromycin,(10) lidocaine,(11) local anesthetic solutions,(12) and total parenteral nutrition (TPN) solutions.(13) In some parenteral formulations, e.g., niacin, sodium bicarbonate is used to produce a sodium salt of the active ingredient that has enhanced solubility. Sodium bicarbonate has also been used as a freeze-drying stabilizer(14) and in toothpastes.

Recently, sodium bicarbonate has been used as a gas-forming agent in alginate raft systems(15–17) and in floating, controlled-release oral dosage forms of furosemide(18) and cisapride.(19) Tablet formulations containing sodium bicarbonate have been shown to increase the absorption of paracetamol,(20,21) and improve the stability of levothyroxine.(22)

Therapeutically, sodium bicarbonate may be used as an antacid, and as a source of the bicarbonate anion in the treatment of metabolic acidosis. Sodium bicarbonate may also be used as a component of oral rehydration salts and as a source of bicarbonate in dialysis fluids.

Sodium bicarbonate is used in food products as an alkali or as a leavening agent, e.g. baking soda. *See* Table I.

Table I: Uses of sodium bicarbonate.

Use	Concentration (%)
Buffer in tablets	10–40
Effervescent tablets	25–50
Isotonic injection/infusion	1.39

8 Description

Sodium bicarbonate occurs as an odorless, white, crystalline powder with a saline, slightly alkaline taste. The crystal structure is monoclinic prisms. Grades with different particle sizes, from a fine powder to free-flowing uniform granules, are commercially available.

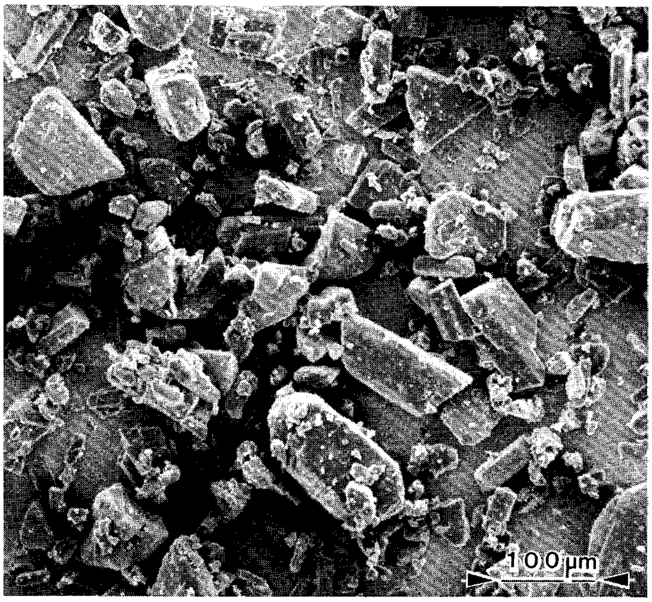
9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Acidity/alkalinity: pH = 8.3 for a freshly prepared 0.1 M aqueous solution at 25°C; alkalinity increases on standing, agitation, or heating.
Density (bulk): 0.869 g/cm^3
Density (tapped): 1.369 g/cm^3
Density(true): 2.173 g/cm^3
Freezing point depression: 0.381°C (1% w/v solution)
Melting point: 270°C (with decomposition)
Moisture content: below 80% relative humidity, the moisture content is less than 1% w/w. Above 85% relative humidity, sodium bicarbonate rapidly absorbs excessive amounts of water and may start to decompose with loss of carbon dioxide.

SEM: 1
Excipient: Sodium bicarbonate
Manufacturer: Merck Ltd.
Magnification: 120×



Osmolarity: a 1.39% w/v aqueous solution is isoosmotic with serum.

Refractive index: n_D^{20} = 1.3344 (1% w/v aqueous solution)

Solubility: *see* Table III.

Table II: Pharmacopeial specifications for sodium bicarbonate.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	—	+	—
Loss on drying	—	—	≤0.25%
Insoluble substances	—	—	+
pH (5% w/v aqueous solution)	7.9–8.4	—	—
Appearance	+	+	—
Carbonate	+	+	≤0.23%(a)
Normal carbonate	—	—	+
Chloride	≤0.04%	≤150 ppm	≤0.015%
Sulfate	—	≤150 ppm	≤0.015%
Ammonia	—	—	+
Ammonium	+	≤20 ppm	—
Aluminum	—	—	≤2 µg/g(a)
Arsenic	≤2 ppm	≤2 ppm	≤2 µg/g
Calcium	—	≤100 ppm	≤0.01%(a)
Magnesium	—	—	≤0.004%(a)
Copper	—	—	≤1 µg/g(a)
Iron	—	≤20 ppm	≤5 µg/g(a)
Heavy metals	≤5 ppm	≤10 ppm	≤5 µg/g
Limit of organics	—	—	+(a)
Organic volatile impurities	—	—	+
Assay (dried basis)	≥99.0%	99.0–101.0%	99.0–100.5%

(a) Where it is labeled as intended for use in hemodialysis.

SEM: 2
Excipient: Sodium bicarbonate
Manufacturer: Merck Ltd.
Magnification: 600×

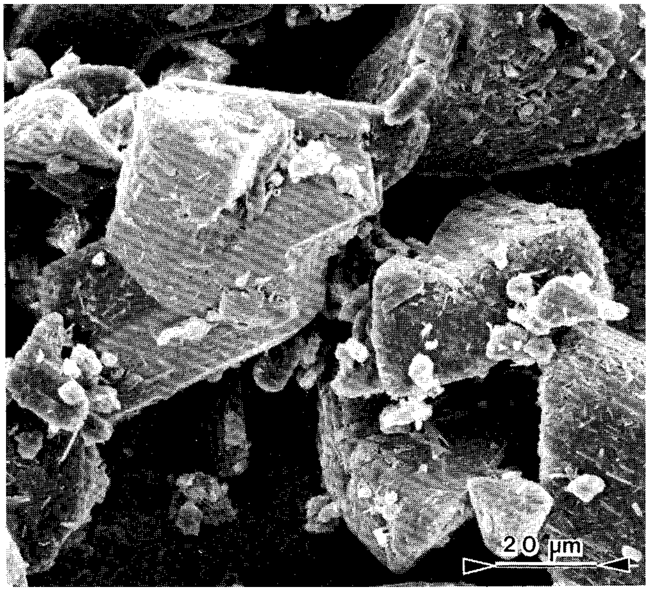


Table III: Solubility of sodium bicarbonate.

Solvent	Solubility at 20°C unless otherwise stated
Ethanol (95%)	Practically insoluble
Ether	Practically insoluble
Water	1 in 11 1 in 4 at 100°C(a) 1 in 10 at 25°C 1 in 12 at 18°C

(a) Note that in hot water, sodium bicarbonate is converted to the carbonate.

11 Stability and Storage Conditions

When heated to about 50°C, sodium bicarbonate begins to dissociate into carbon dioxide, sodium carbonate, and water; on heating to 250–300°C, for a short time, sodium bicarbonate is completely converted into anhydrous sodium carbonate. However, the process is both time- and temperature-dependent, with conversion 90% complete within 75 minutes at 93°C. The reaction proceeds via surface-controlled kinetics; when sodium bicarbonate crystals are heated for a short period of time, very fine needle-shaped crystals of anhydrous sodium carbonate are formed on the sodium bicarbonate surface.(23)

The effects of relative humidity and temperature on the moisture sorption and stability of sodium bicarbonate powder have been investigated. Sodium bicarbonate powder is stable below 76% relative humidity at 25°C and below 48% relative humidity at 40°C.(24) At 54% relative humidity, the degree of pyrolytic decarboxylation of sodium bicarbonate should not exceed 4.5% in order to avoid detrimental effects on stability.(25)

At ambient temperatures, aqueous solutions slowly decompose with partial conversion into the carbonate; the decomposition is accelerated by agitation or heat.

Aqueous solutions of sodium bicarbonate may be sterilized by filtration or autoclaving. To minimize decomposition of sodium bicarbonate by decarboxylation on autoclaving, carbon dioxide is passed through the solution in its final container, which is then hermetically sealed and autoclaved. The sealed container should not be opened for at least 2 hours after it has returned to ambient temperature, to allow time for the complete reformation of the bicarbonate from the carbonate produced during the heating process.

Aqueous solutions of sodium bicarbonate stored in glass containers may develop deposits of small glass particles. Sediments of calcium carbonate with traces of magnesium or other metal carbonates have been found in injections sterilized by autoclaving; these are due to impurities in the bicarbonate or to extraction of calcium and magnesium ions from the glass container. Sedimentation may be retarded by the inclusion of 0.01–0.02% disodium edetate.(26–28)

Sodium bicarbonate is stable in dry air but slowly decomposes in moist air and should therefore be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Sodium bicarbonate reacts with acids, acidic salts, and many alkaloidal salts, with the evolution of carbon dioxide. Sodium bicarbonate can also intensify the darkening of salicylates.

In powder mixtures, atmospheric moisture or water of crystallization from another ingredient is sufficient for sodium bicarbonate to react with compounds such as boric acid or alum. In liquid mixtures containing bismuth subnitrate, sodium bicarbonate reacts with the acid formed by hydrolysis of the bismuth salt.

In solution, sodium bicarbonate has been reported to be incompatible with many drug substances such as ciprofloxacin,(29,30) amiodarone,(31) nicardipine,(32) and levofloxacin.(33)

13 Method of Manufacture

Sodium bicarbonate is manufactured either by passing carbon dioxide into a cold saturated solution of sodium carbonate, or by the ammonia–soda (Solvay) process, in which first ammonia and then carbon dioxide is passed into a sodium chloride solution to precipitate sodium bicarbonate while the more-soluble ammonium chloride remains in solution.

14 Safety

Sodium bicarbonate is used in a number of pharmaceutical formulations including injections and ophthalmic, otic, topical, and oral preparations.

Sodium bicarbonate is metabolized to the sodium cation, which is eliminated from the body by renal excretion, and the bicarbonate anion, which becomes part of the body's bicarbonate store. Any carbon dioxide formed is eliminated via the lungs. Administration of excessive amounts of sodium bicarbonate may thus disturb the body's electrolyte balance, leading to metabolic alkalosis or possibly sodium overload with potentially serious consequences. The amount of sodium present in antacids and effervescent formulations has been sufficient to exacerbate chronic heart failure, especially in elderly patients.(34)

Orally ingested sodium bicarbonate neutralizes gastric acid with the evolution of carbon dioxide and may cause stomach cramps and flatulence.

When used as an excipient, sodium bicarbonate is generally regarded as an essentially nontoxic and nonirritant material.

LD_{50} (mouse, oral): 3.36 g/kg(35)
LD_{50} (rat, oral): 4.22 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (injections; ophthalmic preparations; oral capsules, solutions, and tablets). Included in parenteral (intravenous infusions and injections) and nonparenteral medicines (ear drops; eye lotions; oral capsules, chewable tablets, effervescent powders, effervescent tablets, granules, and tablets; suppositories and suspensions) licensed in the UK.

17 Related Substances

Potassium bicarbonate.

18 Comments

Each gram of sodium bicarbonate represents approximately 11.9 mmol of sodium and of bicarbonate. Each gram of sodium bicarbonate will neutralize 12 mEq of gastric acid in 60 minutes.

The yield of carbon dioxide from sodium bicarbonate is approximately 52% by weight.

Three molecules of sodium bicarbonate are required to neutralize one molecule of citric acid, and two molecules of sodium bicarbonate to neutralize one molecule of tartaric acid. A specification for sodium bicarbonate is contained in the Food Chemicals Codex (FCC).

The EINECS number for sodium bicarbonate is 205-633-8.

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CG Cable.

22 Date of Revision

23 August 2005.

Sodium Borate

1 Nonproprietary Names

BP: Borax
JP: Sodium borate
PhEur: Borax
USPNF: Sodium borate

2 Synonyms

Borax decahydrate; boric acid disodium salt; E285; natrii tetraboras; sodium biborate decahydrate; sodium pyroborate decahydrate; sodium tetraborate decahydrate.

3 Chemical Name and CAS Registry Number

Disodium tetraborate decahydrate [1303-96-4]

4 Empirical Formula and Molecular Weight

$Na_2B_4O_7\cdot 10H_2O$ 381.37

5 Structural Formula

$Na_2B_4O_7\cdot 10H_2O$

6 Functional Category

Alkalizing agent; antimicrobial preservative; buffering agent; disinfectant; emulsifying agent; stabilizing agent.

7 Applications in Pharmaceutical Formulation or Technology

Sodium borate is used in pharmaceutical applications similarly to boric acid (*see* Boric Acid). It has been used externally as a mild astringent and as an emulsifying agent in creams.(1) It has also been used in lozenges, mouthwashes, otic preparations (0.3% w/v), and ophthalmic solutions (0.03–1.0% w/v). Sodium borate has additionally been investigated in the prevention of crystal formation in freeze-dried solutions.(2)

Preparations of sodium borate in honey have historically been used as paints for the throat, tongue, and mouth, but such use is now inadvisable because of concerns about toxicity in such applications, *see* Section 14. Sodium borate is also used in cosmetics such as moisturizers, deodorants, and shampoos.

8 Description

Sodium borate occurs as white, hard crystals, granules, or crystalline powder. It is odorless and efflorescent.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium borate.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Carbonate and bicarbonate	+	—	+
Color of solution	+	+	—
pH	9.1–9.6	9.0–9.6	—
Heavy metals	≤20 ppm	≤25 ppm	≤0.002%
Arsenic	≤5 ppm	≤5 ppm	—
Calcium	—	≤100 ppm	—
Ammonium	—	≤10 ppm	—
Sulfates	—	≤50 ppm	—
Organic volatile impurities	—	—	+
Assay	99.0–103.0%	99.0–103.0%	99.0–105.0%

10 Typical Properties

Acidity/alkalinity: pH = 9.0–9.6 (4% w/v aqueous solution)
Density: 1.73 g/cm^3
Melting point: 75°C when rapidly heated. At 100°C it loses $5H_2O$; at 150°C it loses $9H_2O$; and at 320°C it becomes anhydrous. At about 880°C the substance melts into a glassy state: 'borax beads.'
Solubility: 1 in 1 of glycerin; 1 in 1 of boiling water; 1 in 16 of water; practically insoluble in ethanol (95%), ethanol (99.5%), and diethyl ether.

11 Stability and Storage Conditions

Sodium borate should be stored in a well-closed container in a cool, dry, place. *See also* Section 18.

12 Incompatibilities

Sodium borate is incompatible with acids and with metallic and alkaloidal salts.

13 Method of Manufacture

Sodium borate can be prepared from minerals such as borosodium calcite, pandermite, or tinkal; these are natural sodium or calcium borates. Treatment of the mineral with sodium carbonate and sodium hydrogencarbonate yields the sodium borate decahydrate. In the USA, brine from salt lakes is also an important source of sodium borate.(3)

14 Safety

Sodium borate has weak bacteriostatic and astringent properties. Historically, sodium borate has been used as a disinfectant in skin lotions and eye-, nose-, and mouthwashes. However, boric acid is easily absorbed via mucous membranes and damaged skin, and severe toxicity has been observed, especially in babies and children.(4) Consequently, the use of sodium borate as a disinfectant is now considered somewhat obsolete and careful use is recommended. The toxic effects of sodium borate include vomiting, diarrhea, erythema, CNS depression, and kidney damage. The lethal oral intake is approximately 20 g in adults and 5 g in children.(5)

LD_{50} (guinea pig, oral): 5.33 g/kg(5,6)
LD_{50} (mouse, IP): 2.711 g/kg
LD_{50} (mouse, IV): 1.320 g/kg
LD_{50} (mouse, oral): 2.0 g/kg
LD_{50} (rat, oral): 2.66 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and the quantity of material handled; do not combine with acids.

16 Regulatory Status

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (otic preparations; ophthalmic solutions and suspensions). Included in nonparenteral medicines licensed in the UK, Italy, France, Germany, and Japan. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Boric acid; sodium borate anhydrous.

Sodium borate anhydrous

Synonyms: borax glass; disodium tetraborate anhydrous; fused borax; fused sodium borate; sodium pyroborate; sodium tetraborate anhydrous.
Empirical formula: $Na_2B_4O_7$
Molecular weight: 201.2
CAS number: [1330-43-4]
Boiling point: 1575°C (decomposes)
Melting point: 741°C
Solubility: slightly soluble in glycerin, and water; practically insoluble in ethanol (95%).
Specific gravity: 2.367
Comments: the EINECS number for sodium borate anhydrous is 215-540-4.

18 Comments

Commercially available sodium borate decahydrate is usually present as monoclinic prismatic crystals that become opaque on the surface in dry air. In addition to the decahydrate, a pentahydrate exists; this is also known as 'jeweller's borax.' The anhydrous substance is also available and is called 'pyroborax.'

The EINECS number for sodium borate is 271-536-2.

19 Specific References

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20 General References

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21 Authors

HJ de Jong.

22 Date of Revision

24 August 2005.

Sodium Chloride

1 Nonproprietary Names

BP: Sodium chloride
JP: Sodium chloride
PhEur: Natrii chloridum
USP: Sodium chloride

2 Synonyms

Alberger; chlorure de sodium; common salt; hopper salt; natural halite; rock salt; saline; salt; sea salt; table salt.

3 Chemical Name and CAS Registry Number

Sodium chloride [7647-14-5]

4 Empirical Formula and Molecular Weight

NaCl 58.44

5 Structural Formula

NaCl

6 Functional Category

Tablet and capsule diluent; tonicity agent.

7 Applications in Pharmaceutical Formulation or Technology

Sodium chloride is widely used in a variety of parenteral and nonparenteral pharmaceutical formulations, where the primary use is to produce isotonic solutions.

Sodium chloride has been used as a lubricant and diluent in capsules and direct-compression tablet formulations in the past,(1–5) although this practice is no longer common. Sodium chloride has also been used as a channeling agent(6,7) and as an osmotic agent(8,9) in the cores of controlled-release tablets. It has been used as a porosity modifier in tablet coatings,(10) and to control drug release from microcapsules.(11,12)

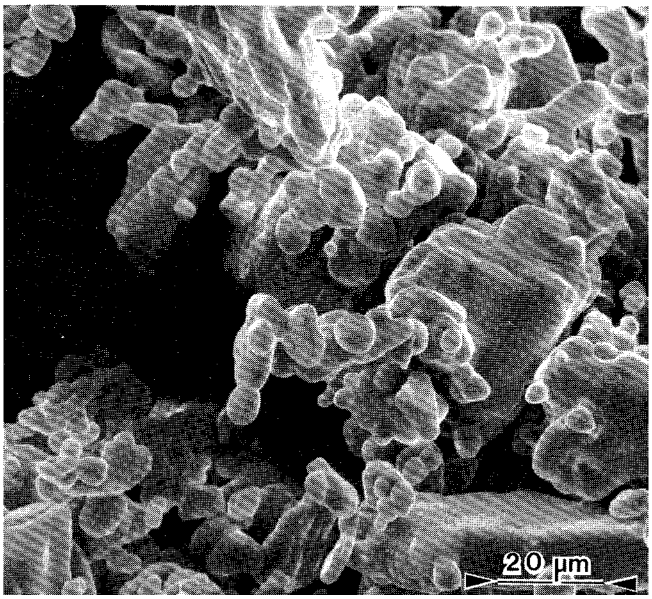
The addition of sodium chloride to aqueous spray-coating solutions containing hydroxypropyl cellulose or hypromellose suppresses the agglomeration of crystalline cellulose particles.(13) Sodium chloride can also be used to modify drug release from gels(14) and from emulsions.(15) It can be used to control micelle size,(16–18) and to adjust the viscosity of polymer dispersions by altering the ionic character of a formulation.(19,20)

See Table I.

Table I: Uses of sodium chloride.

Use	Concentration (%)
Capsule diluent	10–80
Controlled flocculation of suspensions	$\leqslant 1$
Direct compression tablet diluent	10–80
To produce isotonic solutions in intravenous or ophthalmic preparations	$\leqslant 0.9$
Water-soluble tablet lubricant	5–20

SEM: 1
Excipient: Sodium chloride, powder
Manufacturer: Mallinckrodt Speciality Chemicals Co.
Magnification: 600×



8 Description

Sodium chloride occurs as a white crystalline powder or colorless crystals; it has a saline taste. The crystal lattice is a face-centered cubic structure. Solid sodium chloride contains no water of crystallization although, below 0°C, salt may crystallize as a dihydrate.

9 Pharmacopeial Specifications

See Table II.

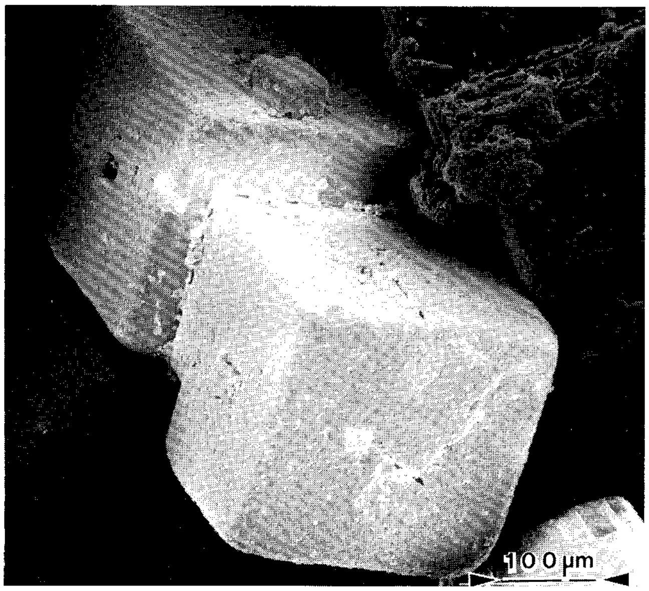
Table II: Pharmacopeial specifications for sodium chloride.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	+	+	—
Appearance of solution	+	+	+
Acidity or alkalinity	+	+	+
Loss on drying	⩽0.5%	⩽0.5%	0.5%
Arsenic	⩽2 ppm	⩽1 ppm	1 μg/g
Bromides	+	⩽100 ppm	⩽0.01%
Chloride	—	—	+
Barium	+	+	+
Nitrites	—	+	+
Aluminum	—	⩽0.2 ppm[a]	⩽0.2 μg/g[a]
Calcium and magnesium	+	—	—
Magnesium and alkaline earth metals	+	⩽100 ppm	⩽0.01%
Iodide	+	+	+
Iron	+	⩽2 ppm	⩽2 μg/g
Sulfate	+	⩽200 ppm	⩽0.020%
Ferrocyanides	+	+	+
Heavy metals	⩽3 ppm	⩽5 ppm	⩽5 ppm
Phosphate	+	⩽25 ppm	⩽0.0025%
Potassium	—	⩽500 ppm[a][b]	⩽0.05%[a][b]
Organic volatile impurities	—	—	—
Sterility	—	—	+
Bacterial endotoxins	—	⩽5 IU/g[b]	—
Assay (dried basis)	99.0–100.5%	99.0–100.5%	99.5–100.5%

[a] If for use in peritoneal dialysis, hemodialysis or hemofiltration solutions.

[b] If for parenteral use.

SEM: 2
Excipient: Sodium chloride, granular
Manufacturer: Van Waters & Rogers, Inc.
Magnification: 120×



10 Typical Properties

Acidity/alkalinity: pH = 6.7–7.3 (saturated aqueous solution)
Angle of repose: 38° for cubic crystals
Boiling point: 1413°C
Compressibility: with sodium chloride powder of less than 30 μm particle size, tablets are formed by plastic deformation; above this size, both plastic deformation and fracture occur.(1,3,4) *See also* Figure 1.
Density:
2.17 g/cm^3;
1.20 g/cm^3 for saturated aqueous solution.
Density (bulk): 0.93 g/cm^3
Density (tapped): 1.09 g/cm^3
Dielectric constant: 5.9 at 1 MHz
Freezing point depression: *see* Table III.

Table III: Freezing point depression values of aqueous sodium chloride.

Aqueous sodium chloride solution (% w/v)	Freezing point depression (°C)
11.69	6.90
17.53	10.82
23.38	15.14
30.39	21.12

Hardness (Mohs): 2–2.5
Hygroscopicity: hygroscopic above 75% relative humidity.
Melting point: 804°C
Osmolarity: a 0.9% w/v aqueous solution is iso-osmotic with serum.
Refractive index: n_D^{20} = 1.343 for a 1 M aqueous solution.
Solubility: *see* Table IV.

Table IV: Solubility of sodium chloride.

Solvent	Solubility at 20°C unless otherwise stated
Ethanol	Slightly soluble
Ethanol (95%)	1 in 250
Glycerin	1 in 10
Water	1 in 2.8
	1 in 2.6 at 100°C

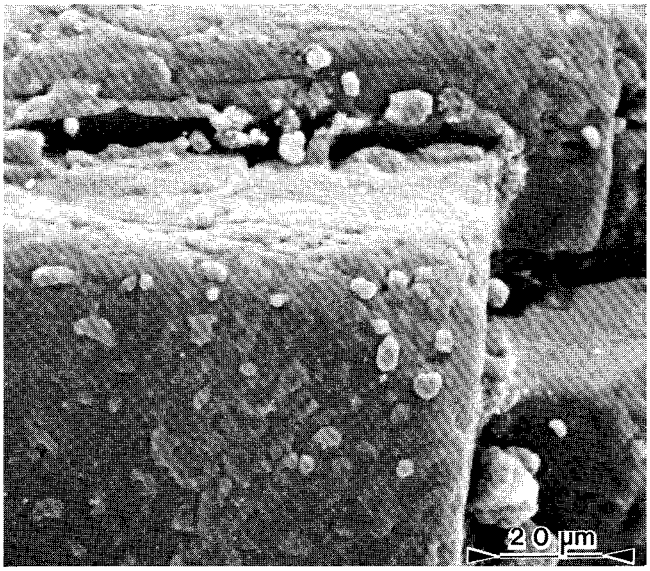
Thermal conductivity: 1.15 Wm/K at 273 K
Specific heat capacity: 854 J/kg/K
Vapor pressure:
133.3 Pa at 865°C for solid;
1759.6 Pa at 20°C for a saturated aqueous solution (equivalent to 75.3% relative humidity).
Viscosity: a 10% w/v solution has a viscosity of 1.19 mPa s (1.19 cP).

11 Stability and Storage Conditions

Aqueous sodium chloride solutions are stable but may cause the separation of glass particles from certain types of glass containers. Aqueous solutions may be sterilized by autoclaving or filtration. The solid material is stable and should be stored in a well-closed container, in a cool, dry place.

It has been shown that the compaction characteristics and the mechanical properties of tablets are influenced by the relative humidity of the storage conditions under which sodium chloride was stored.(21,22)

SEM: 3
Excipient: Sodium chloride, granular
Manufacturer: Van Waters & Rogers, Inc.
Magnification: 600×



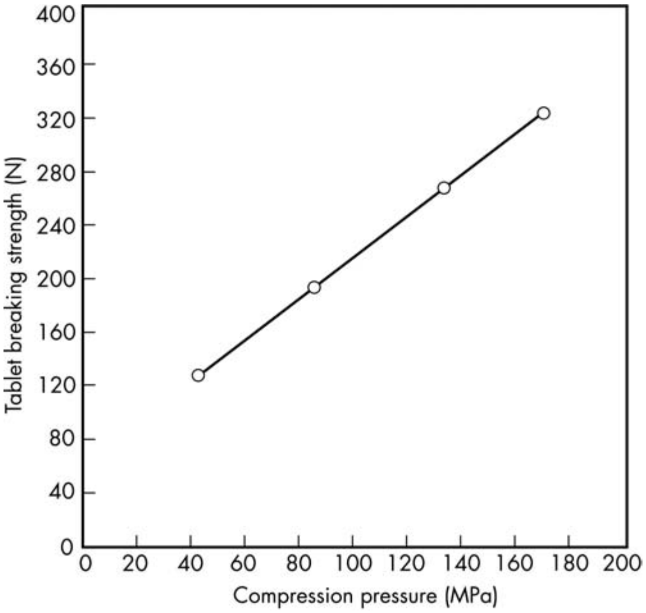


Figure 1: Compression characteristics of sodium chloride (cubic crystals).(3) Tablet diameter = 12 mm.

12 Incompatibilities

Aqueous sodium chloride solutions are corrosive to iron. They also react to form precipitates with silver, lead, and mercury salts. Strong oxidizing agents liberate chlorine from acidified solutions of sodium chloride. The solubility of the antimicrobial preservative methylparaben is decreased in aqueous sodium chloride solutions(23) and the viscosity of carbomer gels and solutions of hydroxyethyl cellulose or hydroxypropyl cellulose is reduced by the addition of sodium chloride.

13 Method of Manufacture

Sodium chloride occurs naturally as the mineral halite. Commercially, it is obtained by the solar evaporation of sea water, by mining, or by the evaporation of brine from underground salt deposits.

14 Safety

Sodium chloride is the most important salt in the body for maintaining the osmotic tension of blood and tissues. About 5–12 g of sodium chloride is consumed daily, in the normal adult diet, and a corresponding amount is excreted in the urine. As an excipient, sodium chloride may be regarded as an essentially nontoxic and nonirritant material. However, toxic effects following the oral ingestion of 0.5–1.0 g/kg body-weight in adults may occur. The oral ingestion of larger quantities of sodium chloride, e.g. 1000 g in 600 mL of water,(24) is harmful and can induce irritation of the gastrointestinal tract, vomiting, hypernatremia, respiratory distress, convulsions, or death.

In rats, the minimum lethal intravenous dose is 2.5 g/kg body-weight.

LD_{50} (mouse, IP): 6.61 g/kg(25)
LD_{50} (mouse, IV): 0.65 g/kg
LD_{50} (mouse, oral): 4.0 g/kg
LD_{50} (mouse, SC): 3.0 g/kg
LD_{50} (rat, oral): 3.0 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. If heated to high temperatures, sodium chloride evolves a vapor irritating to the eyes.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (injections; inhalations; nasal, ophthalmic, oral, otic, rectal, and topical preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Potassium chloride.

18 Comments

Domestic table salt may contain sodium iodide (as a prophylactic substance against goiter) and agents such as magnesium carbonate, calcium phosphate, or starch, which reduce the hygroscopic characteristics of the salt and maintain the powder in a free-flowing state.

Food-grade dendritic salt, which is porous, can be used as an absorbent for liquid medications, and as a tablet diluent in specific formulations.

Each gram of sodium chloride represents approximately 17.1 mmol of sodium and 17.1 mmol of chloride; 2.54 g of sodium chloride is approximately equivalent to 1 g of sodium.

A saturated solution of sodium chloride can be used as a constant-humidity solution; at 25°C, a relative humidity of 75% is produced. A specification for sodium chloride is contained in the Food Chemicals Codex (FCC).

The EINECS number for sodium chloride is 231-598-3.

19 Specific References

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18 McDonald C, Richardson C. The effect of added salts on solubilization by a non-ionic surfactant. *J Pharm Pharmacol* 1981; **33**: 38–39.

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22 Ahlneck C, Alderborn G. Moisure adsorption and tabletting. II. The effect on tensile strength and air permeability of the relative humidity during storage of tablets of 3 crystalline materials. *Int J Pharm* 1989; **56**: 143–150.

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20 General References

Heng PW, Hao JS, Chan LW, Chen SH. Influence of osmotic agents in diffusion layer on drug release from multilayer coated pellets. *Drug Dev Ind Pharm* 2004; **30**(2): 213–220.

21 Authors

SC Owen.

22 Date of Revision

8 June 2005.

Sodium Citrate Dihydrate

1 Nonproprietary Names

BP: Sodium citrate
JP: Sodium citrate
PhEur: Natrii citras
USP: Sodium citrate

2 Synonyms

Citric acid trisodium salt; E331; sodium citrate tertiary; trisodium citrate.

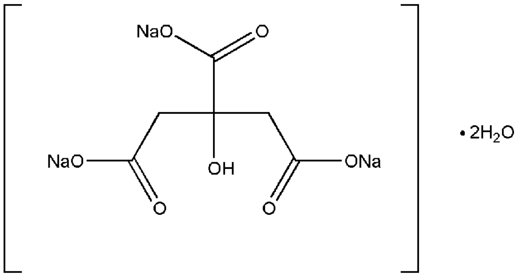
3 Chemical Name and CAS Registry Number

Trisodium 2-hydroxypropane-1,2,3-tricarboxylate dihydrate [6132-04-3]

4 Empirical Formula and Molecular Weight

$C_6H_5Na_3O_7{\cdot}2H_2O$ 294.10

5 Structural Formula



6 Functional Category

Alkalizing agent; buffering agent; emulsifier; sequestering agent.

7 Applications in Pharmaceutical Formulation or Technology

Sodium citrate, as either the dihydrate or anhydrous material, is widely used in pharmaceutical formulations; *see* Table I.

It is used in food products, primarily to adjust the pH of solutions. It is also used as a sequestering agent. The anhydrous material is used in effervescent tablet formulations.(1) Sodium citrate is additionally used as a blood anticoagulant either alone or in combination with other citrates such as disodium hydrogen citrate.

Therapeutically, sodium citrate is used to relieve the painful irritation caused by cystitis, and also to treat dehydration and acidosis due to diarrhea; *see* Section 14.

Table I: Uses of sodium citrate dihydrate.

Use	Concentration (%)
Buffering agent	0.3–2.0
Injections	0.02–4.0
Ophthalmic solutions	0.1–2.0
Sequestering agent	0.3–2.0

8 Description

Sodium citrate dihydrate consists of odorless, colorless, monoclinic crystals, or a white crystalline powder with a cooling, saline taste. It is slightly deliquescent in moist air, and in warm dry air it is efflorescent. Although most pharmacopeias specify that sodium citrate is the dihydrate, the USP 28 states that sodium citrate may be either the dihydrate or anhydrous material.

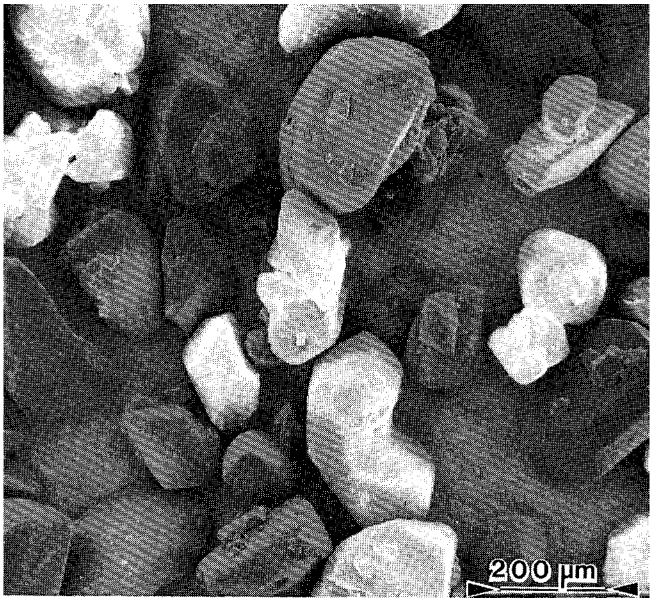
9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Acidity/alkalinity: pH = 7.0–9.0 (5% w/v aqueous solution)
Density (bulk): 1.12 g/cm^3
Density (tapped): 0.99 g/cm^3
Density (true): 1.19 g/cm^3
Melting point: converts to the anhydrous form at 150°C.

SEM: 1
Excipient: Sodium citrate dihydrate (granular)
Manufacturer: Pfizer Ltd
Magnification: 60×



SEM: 2
Excipient: Sodium citrate dihydrate (granular)
Manufacturer: Pfizer Ltd
Magnification: 600×

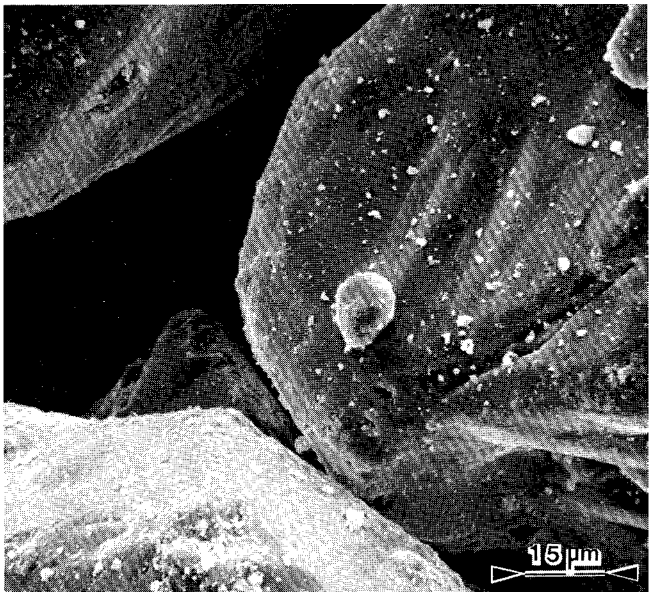


Table II: Pharmacopeial specifications for sodium citrate dihydrate.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	—	+	—
pH	7.5–8.5	—	—
Appearance of solution	+	+	—
Acidity or alkalinity	+	+	+
Loss on drying	10.0–13.0%	—	—
Water	—	11.0–13.0%	10.0–13.0%
Oxalate	+	≤300 ppm	—
Sulfate	≤0.048%	≤150 ppm	—
Heavy metals	≤10 ppm	≤10 ppm	≤0.001%
Arsenic	≤2 ppm	—	—
Chloride	≤0.015%	≤50 ppm	—
Tartrate	+	—	+
Readily carbonizable substances	+	+	—
Pyrogens	—	+[a]	—
Assay (anhydrous basis)	≥99.0%	99.0–101.0%	99.0–100.5%

[a] If intended for use in large-volume preparations for parenteral use, compliance with a test for pyrogens may be required.

Osmolarity: a 3.02% w/v aqueous solution is iso-osmotic with serum.

Particle size distribution: various grades of sodium citrate dihydrate with different particle sizes are commercially available.

Solubility: soluble 1 in 1.5 of water, 1 in 0.6 of boiling water; practically insoluble in ethanol (95%).

11 Stability and Storage Conditions

Sodium citrate dihydrate is a stable material. Aqueous solutions may be sterilized by autoclaving. On storage, aqueous solutions may cause the separation of small, solid particles from glass containers.

The bulk material should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Aqueous solutions are slightly alkaline and will react with acidic substances. Alkaloidal salts may be precipitated from their aqueous or hydro-alcohol solutions. Calcium and strontium salts will cause precipitation of the corresponding citrates. Other incompatibilities include bases, reducing agents, and oxidizing agents.

13 Method of Manufacture

Sodium citrate is prepared by adding sodium carbonate to a solution of citric acid until effervescence ceases. The resulting solution is filtered and evaporated to dryness.

14 Safety

After ingestion, sodium citrate is absorbed and metabolized to bicarbonate. Although it is generally regarded as a nontoxic and nonirritant excipient, excessive consumption may cause gastrointestinal discomfort or diarrhea. Therapeutically, in adults, up to 15 g daily of sodium citrate dihydrate may be administered orally, in divided doses, as an aqueous solution to relieve the painful irritation caused by cystitis.

Citrates and citric acid enhance intestinal aluminum absorption in renal patients, which may lead to increased, harmful serum aluminum levels. It has therefore been suggested that patients with renal failure taking aluminum compounds to control phosphate absorption should not be prescribed citrate- or citric acid-containing products.(2)

See Section 17 for anhydrous sodium citrate animal toxicity data.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium citrate dihydrate dust may be irritant to the eyes and respiratory tract. Eye protection and gloves are recommended. Sodium citrate should be handled in a well-ventilated environment or a dust mask should be worn.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (inhalations, injections, ophthalmic products, oral solutions, suspensions, syrups and tablets, nasal, otic, rectal, topical, transdermal, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Anhydrous sodium citrate; citric acid monohydrate.

Anhydrous sodium citrate

Empirical formula: $C_6H_5Na_3O_7$

Molecular weight: 258.07

CAS number: [68-04-2]

Synonyms: anhydrous trisodium citrate; citric acid trisodium salt anhydrous; trisodium 2-hydroxy-1,2,3-propanetricarboxylic acid.

Appearance: colorless crystals or a white crystalline powder.

Safety:

LD_{50} (mouse, IP): 1.36 g/kg(3)
LD_{50} (mouse, IV): 0.17 g/kg
LD_{50} (rabbit, IV): 0.45 g/kg
LD_{50} (rat, IP): 1.55 g/kg

18 Comments

Each gram of sodium citrate dihydrate represents approximately 10.2 mmol of sodium and 3.4 mmol of citrate. Each gram of anhydrous sodium citrate represents approximately 11.6 mmol of sodium and 3.9 mmol of citrate.

The EINECS number for sodium citrate is 200-675-3.

19 Specific References

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3 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 2572.

20 General References

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21 Authors

GE Amidon.

22 Date of Revision

19 August 2005.

Sodium Cyclamate

1 Nonproprietary Names

BP: Sodium cyclamate
PhEur: Natrii cyclamas

2 Synonyms

Cyclohexylsulfamic acid monosodium salt; E952; sodium cyclohexanesulfamate.

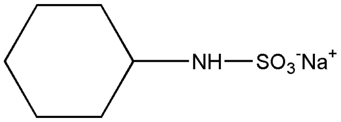
3 Chemical Name and CAS Registry Number

Sodium *N*-cyclohexylsulfamate [139-05-9]

4 Empirical Formula and Molecular Weight

$C_6H_{12}NNaO_3S$ 201.22

5 Structural Formula



6 Functional Category

Sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

Sodium cyclamate is used as an intense sweetening agent in pharmaceutical formulations, foods, beverages, and table-top sweeteners. In dilute solution, up to about 0.17% w/v, the sweetening power is approximately 30 times that of sucrose. However, at higher concentrations this is reduced and at a concentration of 0.5% w/v a bitter taste becomes noticeable. Sodium cyclamate enhances flavor systems and can be used to mask some unpleasant taste characteristics. In most applications, sodium cyclamate is used in combination with saccharin.

8 Description

Sodium cyclamate occurs as white, odorless or almost odorless crystals or as a crystalline powder with an intensely sweet taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium cyclamate.

Test	PhEur 2005
Identification	+
Characters	+
Appearance of solution	+
pH (10% w/v aqueous solution)	5.5–7.5
Absorbance at 270 nm	⩽0.10
Sulfamic acid	+
Aniline	⩽1 ppm
Cyclohexylamine	⩽10 ppm
Dicyclohexylamine	⩽1 ppm
Sulfates	⩽0.1%
Heavy metals	⩽10 ppm
Loss on drying	⩽1.0%
Assay (dried basis)	98.5–101.0%

10 Typical Properties

Acidity/alkalinity: pH = 5.5–7.5 for a 10% w/v aqueous solution.
Solubility: *see* Table II.

Table II: Solubility of sodium cyclamate.

Solvent	Solubility at 20°C unless otherwise stated
Benzene	Practically insoluble
Chloroform	Practically insoluble
Ethanol (95%)	1 in 250
Ether	Practically insoluble
Propylene glycol	1 in 25
Water	1 in 5 1 in 2 at 45°C

11 Stability and Storage Conditions

Sodium cyclamate is hydrolyzed by sulfuric acid and cyclohexylamine at a very slow rate that is proportional to the hydrogen ion concentration. Therefore, for all practical considerations, it can be regarded as stable. Solutions are also stable to heat, light, and air over a wide pH range.

Samples of tablets containing sodium cyclamate and saccharin have shown no loss in sweetening power following storage for up to 20 years.

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

—

13 Method of Manufacture

Cyclamates are prepared by the sulfonation of cyclohexylamine in the presence of a base. Commercially, the sulfonation can involve sulfamic acid, a sulfate salt, or sulfur trioxide. Tertiary bases such as triethylamine or trimethylamine may be used as the condensing agent. The amine salts of cyclamate that are produced are converted to the sodium, calcium, potassium, or magnesium salt by treatment with the appropriate metal oxide.

14 Safety

There has been considerable controversy concerning the safety of cyclamate following the FDA decision in 1970 to ban its use in the USA.(1–3) This decision resulted from a feeding study in rats that suggested that cyclamate could cause an unusual form of bladder cancer. However, that study has been criticized because it involved very high doses of cyclamate administered with saccharin, which has itself been the subject of controversy concerning its safety; *see* Saccharin. Although excreted almost entirely unchanged in the urine, a potentially harmful metabolite of sodium cyclamate, cyclohexylamine, has been detected in humans.(4)

Extensive long-term animal feeding studies and epidemiological studies in humans have failed to show any evidence that cyclamate is carcinogenic or mutagenic.(5,6) As a result, sodium cyclamate is now accepted in many countries for use in foods and pharmaceutical formulations. *See also* Section 16.

Few adverse reactions to cyclamate have been reported, although its use has been associated with instances of photosensitive dermatitis.(7)

The WHO has set an estimated acceptable daily intake for sodium and calcium cyclamate, expressed as cyclamic acid, at up to 11 mg/kg body-weight.(8) In Europe, a temporary acceptable daily intake for sodium and calcium cyclamate, expressed as cyclamic acid, has been set at up to 1.5 mg/kg body-weight.

LD_{50} (mouse, IP): 1.15 g/kg(9)
LD_{50} (mouse, IV): 4.8 g/kg
LD_{50} (mouse, oral): 17 g/kg
LD_{50} (rat, IP): 1.35 g/kg
LD_{50} (rat, IV): 3.5 g/kg
LD_{50} (rat, oral): 15.25 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended.

16 Regulatory Status

The use of cyclamates as artificial sweetners in food, soft drinks, and artificial sweetening tablets was at one time prohibited in the UK and some other countries owing to concern about the metabolite cyclohexylamine. However, this is no longer the case, and cyclamates are now permitted for use as a food additive in Europe.

Included in the FDA Inactive Ingredients Guide (oral powder, solutions and suspensions). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Alitame; calcium cyclamate; cyclamic acid.

Calcium cyclamate

Empirical formula: $C_{12}H_{24}CaN_2O_6S_2 \cdot 2H_2O$
Molecular weight: 432.57
CAS number:
[5897-16-5] for the dihydrate;
[139-06-0] for the anhydrous form.
Synonyms: calcium *N*-cyclohexylsulfamate dihydrate; *Cyclan*; cyclohexanesulfamic acid calcium salt; cyclohexylsulfamic acid calcium salt; E952; *Sucaryl calcium*.
Appearance: white, odorless or almost odorless crystals or a crystalline powder with an intensely sweet taste.
Acidity/alkalinity: pH = 5.5–7.5 for a 10% w/v aqueous solution.
Solubility: freely soluble in water; practically insoluble in benzene, chloroform, ethanol (95%), and ether.

Cyclamic acid

Empirical formula: $C_6H_{13}NO_3S$
Molecular weight: 179.23
CAS number: [100-88-9]
Synonyms: cyclamate; cyclohexanesulfamic acid; *N*-cyclohexylsulfamic acid; E952; hexamic acid; *Sucaryl*.
Appearance: white, odorless or almost odorless crystals or a crystalline powder with an intensely sweet taste.
Melting point: 169–170°C
Solubility: slightly soluble in water.

18 Comments

The perceived intensity of sweeteners relative to sucrose depends upon their concentration, temperature of tasting, and pH, and on the flavor and texture of the product concerned.

Intense sweetening agents will not replace the bulk, textural, or preservative characteristics of sucrose if sucrose is removed from a formulation.

Synergistic effects for combinations of sweeteners have been reported, e.g., sodium cyclamate with saccharin sodium or acesulfame potassium.

Sodium cyclamate has also been used to increase the solubility of neohesperidin dihydrochalcone in sweetener blends.(10)

19 Specific References

1 Nabors LO, Miller WT. Cyclamate: a toxicological review. *Commen Toxicol* 1989; 3(4): 307–315.
2 Lecos C. The sweet and sour history of saccharin, cyclamate and aspartame. *FDA Consumer* 1981; **15**(7): 8–11.
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4 Kojima S, Ichibagase H. Studies on synthetic sweetening agents VIII. Cyclohexylamine, a metabolite of sodium cyclamate. *Chem Pharm Bull* 1966; **14**: 971–974.
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6 Schmähl D, Habs M. Investigations on the carcinogenicity of the artificial sweeteners sodium cyclamate and sodium saccharin in rats in a two-generation experiment. *Arzneimittelforschung* 1984; **34**: 604–606.
7 Yong JM, Sanderson KV. Photosensitive dermatitis and renal tubular acidosis after ingestion of calcium cyclamate. *Lancet* 1969; **ii**: 1273–1274.
8 FAO/WHO. Evaluation of certain food additives and contaminants. Twenty-sixth report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1982; No. 683.
9 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 3243.

10 Benavente-Garcia O, Castillo J, Del Bano MJ, Lorente J. Improved water solubility of neohesperidin dihydrochalcone in sweetener blends. *J Agric Food Chem* 2001; **49**(1): 189–191.

20 General References

Anonymous. Saccharin is safe. *Chem Br* 2001; **37**(4): 18.
Schiffman SS, Sattely-Miller EA, Graham BG, *et al*. Effect of temperature, pH, and ions on sweet taste. *Physiol Behav* 2000; **68**(4): 469–481.

21 Authors

SC Owen.

22 Date of Revision

11 August 2005.

Sodium Hyaluronate

1 Nonproprietary Names

BP: Sodium hyaluronate
PhEur: Natrii hyaluronas

2 Synonyms

Hyaluronan; hyaluronate sodium; *RITA HA C-1-C.*

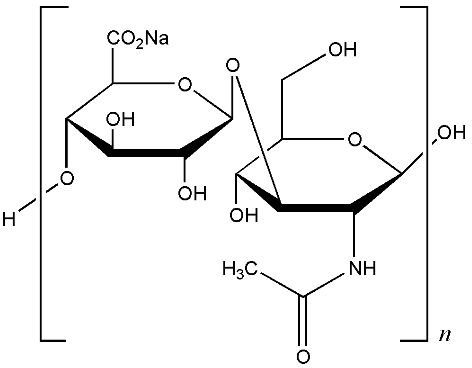
3 Chemical Name and CAS Registry Number

Sodium hyaluronate [9067-32-7]

4 Empirical Formula and Molecular Weight

$(C_{14}H_{20}NO_{11}Na)_n$ (401.3)*n*

5 Structural Formula



6 Functional Category

Humectant; lubricant; matrix for sustained release.

7 Applications in Pharmaceutical Formulation or Technology

Sodium hyaluronate is the predominant form of hyaluronic acid at physiological pH. The name hyaluronan is used when the polysaccharide is mentioned in general terms, and in the literature the terms hyaluronic acid and sodium hyaluronate are used interchangeably.

Hyaluronan is used therapeutically to treat osteoarthritis in the knee, and is an effective treatment for arthritic pain.(1) Crosslinked hyaluronan gels are used as drug delivery systems.(2)

Hyaluronan is the most common negatively charged glycosaminoglycan in the human vitreous humor, and is known to interact with polymeric and liposomal DNA complexes,(3) where hyaluronan solutions have been shown to decrease the cellular uptake of complexes.(4) This is useful for enhancing the availability and retention time of drugs administered to the eye. It is immunoneutral, which makes it useful for the attachment of biomaterials for use in tissue engineering and drug delivery systems;(5) it also has important applications in the fields of vascosurgery and vascosupplementation.(6)

8 Description

The PhEur 2005 describes sodium hyaluronate as the sodium salt of hyaluronic acid, a glycosaminoglycan consisting of D-glucuronic acid and *N*-acetyl-D-glucosamine disaccharide units.

Sodium hyaluronate occurs as white to off-white powder or granules. It is very hygroscopic.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specification for sodium hyaluronate.

Test	PhEur 2005
Characters	+
Identification	+
Appearance of solution	+
pH	5.0–8.5
Intrinsic viscosity	+
Sulfated glycosaminoglycans	$\leqslant 1\%$
Nucleic acids	$\leqslant 0.5$
Protein	$\leqslant 0.3\%$[a]
Chlorides	$\leqslant 0.5\%$
Iron	$\leqslant 80$ ppm
Loss on drying	$\leqslant 20.0\%$
Microbial contamination	$\leqslant 10^2$/g
Bacterial endotoxins	$\leqslant 0.05$ IU/mg[b]
Assay	95.0–105.0%

[a] <0.1% for parenteral dosage forms.

[b] $\leqslant 0.5$ IU/mg for parenteral dosage forms.

10 Typical Properties

Acidity/alkalinity: pH = 5.0–8.5 (0.5% w/v aqueous solution)

Solubility: soluble in water, although speed of dissolution depends upon molecular weight (higher molecular weights are slower to dissolve, although this process can be increased by gentle agitation). Slightly soluble in mixtures of organic solvents with water.(7)

11 Stability and Storage Conditions

Sodium hyaluronate should be stored in a cool, dry place in tightly sealed containers. The powder is stable for three years if stored in unopened containers.

12 Incompatibilities

—

13 Method of Manufacture

Sodium hyaluronate occurs naturally in vitreous humor, serum, chicken combs, shark skin, and whale cartilage; it is usually extracted and purified from chicken combs. It may also be manufactured by fermentation of selected *Streptococcus zooepidemicus* bacterial strains; sodium hyaluronate is removed from the fermentation medium by filtration and purified by ultrafiltration. It is then precipitated with an organic solvent and dried.

14 Safety

Sodium hyaluronate is used in cosmetics and in topical, parenteral, and ophthalmic pharmaceutical formulations. It is generally regarded as a relatively nontoxic and nonirritant material. Sodium hyaluronate has been reported to be an experimental teratogen.(8)

LD_{50} (mouse, IP): 1.5 g/kg(8)
LD_{50} (rabbit, IP): 1.82 g/kg
LD_{50} (rat, IP): 1.77 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. When heated to decomposition, sodium hyaluronate emits toxic fumes of Na_2O.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (topical gel preparation).

17 Related Substances

Hyaluronic acid.

Hyaluronic acid

Molecular weight: hyaluronic acid molecules have a molecular weight of 300–2000 kDa as the number of repeating disaccharide units in each molecule is variable. In its natural form, hyaluronic acid exists as a high-molecular-weight polymer of 10^6–10^7 Da.

CAS number: [9067-32-7]

Appearance: hyaluronic acid appears as a white to off-white powder or granules.

Comments: hyaluronic acid is used as an adjuvant for ophthalmic drug delivery,(9) and has been found to enhance the absorption of drugs and proteins via mucosal tissue.(10) It has also been used experimentally in controlled-release films that are suitable for application to surgical sites for the prevention of adhesion formation,(11) and in matrix formulations used in gene delivery systems.(12) The EINECS number for hyaluronic acid is 232-678-0.

18 Comments

Microspheres prepared from hyaluronan esters have been evaluated for the vaginal administration of calcitonin in the treatment of postmenopausal osteoporosis.(13) Microspheres prepared from hyaluronan esters have also been used experimentally as delivery devices for nerve growth factors,(14) and as a nasal delivery system for insulin.(15)

An *N*-(2-hydroxypropyl)methacrylamide (HPMA)–hyaluronan polymeric drug delivery system has been used for the targeted delivery of doxorubicin to cancer cells. This copolymer exhibited increased toxicity due to hyaluronan receptor-mediated uptake of the macromolecular drug.(16)

The EINECS number for sodium hyaluronate is232-678-0.

19 Specific References

1 Castellacci E, Polieri T. Antalgesic effect and clinical tolerability of hyaluronic acid in patients with degenerative diseases of knee cartilage: an outpatient treatment survey. *Drugs Exp Clin Res* 2004; **30**(2): 67–73.
2 Dehayza P, Cheng L. Sodium hyaluronate microspheres. US Patent No. 2,004,127,459; 2004.
3 Pitkänen L, Ruponen M, Nieminen J, Urtti A. Vitreous is a barrier in nonviral gene transfer by cationic lipids and polymers. *Pharm Res* 2003; **20**(4): 576–583.
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10 Cho KY, Chung TW, Kim BC, *et al*. Release of ciprofloxacin from polymer-graft-hyaluronic acid hydrogels *in vitro*. *Int J Pharm* 2003; **260**(1): 83–91.
11 Jackson JK, Skinner KC, Burgess L, *et al*. Paclitaxel-loaded crosslinked hyaluronic acid films for the prevention of postsurgical adhesions. *Pharm Res* 2002; **19**(4): 411–417.
12 Kim A, Checkla DM, Dehazya P, *et al*. Characterization of DNA-hyaluronan matrix for sustained gene transfer. *J Control Release* 2003; **90**(1): 81–75.
13 Rochira M, Miglietta MR, Richardson JL, *et al*. Novel vaginal delivery systems for calcitonin II. Preparation and characterisation of HYAFF® microspheres containing calcitonin. *Int J Pharm* 1996; **144**: 19–26.
14 Ghezzo E, Beredetti LM, Rochira M, *et al*. Hyaluronan derivative microspheres as NGF delivery devices: preparation methods and *in vitro* release characterization. *Int J Pharm* 1992; **29**: 133–141.
15 Illum L, Farray NF, Fisher AN, *et al*. Hyaluronic acid ester microspheres as a nasal delivery system for insulin. *J Control Release* 1994; **29**: 133–141.
16 Luo Y, Bernshaw NJ, Lu ZR, *et al*. Targetted delivery of doxorubicin by HPMA copolymer–hyaluronan bioconjugates. *Pharm Res* 2002; **19**(4): 396–402.

20 General References

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21 Authors

SC Owen.

22 Date of Revision

26 May 2005.

Sodium Hydroxide

1 Nonproprietary Names

BP: Sodium hydroxide
JP: Sodium hydroxide
PhEur: Natrii hydroxidum
USPNF: Sodium hydroxide

2 Synonyms

Caustic soda; E524; lye; soda lye; sodium hydrate.

3 Chemical Name and CAS Registry Number

Sodium hydroxide [1310-73-2]

4 Empirical Formula and Molecular Weight

NaOH 40.00

5 Structural Formula

NaOH

6 Functional Category

Alkalizing agent; buffering agent.

7 Applications in Pharmaceutical Formulation or Technology

Sodium hydroxide is widely used in pharmaceutical formulations to adjust the pH of solutions.(1) It can also be used to react with weak acids to form salts.

8 Description

Sodium hydroxide occurs as a white or nearly white fused mass. It is available in small pellets, flakes, sticks, and other shapes or forms. It is hard and brittle and shows a crystalline fracture. Sodium hydroxide is very deliquescent and on exposure to air it rapidly absorbs carbon dioxide and water.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium hydroxide.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	–	+	–
Appearance of solution	+	+	–
Insoluble substances and organic matter	–	–	+
Sodium carbonate	⩽2.0%	⩽2.0%	–
Sulfates	–	⩽50 ppm	–
Chlorides	⩽0.05%	⩽50 ppm	–
Iron	–	⩽10 ppm	–
Mercury	+	–	–
Heavy metals	⩽30 ppm	⩽20 ppm	⩽0.003%
Potassium	+	–	+
Assay (total alkali calculated as NaOH)	⩾95.0%	97.0–100.5%	95.0–100.5%

10 Typical Properties

Acidity/alkalinity:
pH ≈ 12 (0.05% w/w aqueous solution);
pH ≈ 13 (0.5% w/w aqueous solution);
pH ≈ 14 (5% w/w aqueous solution).
Melting point: 318°C
Solubility: *see* Table II.

Table II: Solubility of sodium hydroxide.

Solvent	Solubility at 20°C unless otherwise stated
Ethanol	1 in 7.2
Ether	Practically insoluble
Glycerin	Soluble
Methanol	1 in 4.2
Water	1 in 0.9
	1 in 0.3 at 100°C

11 Stability and Storage Conditions

Sodium hydroxide should be stored in an airtight nonmetallic container in a cool, dry place. When exposed to air, sodium hydroxide rapidly absorbs moisture and liquefies, but subsequently becomes solid again owing to absorption of carbon dioxide and formation of sodium carbonate.

12 Incompatibilities

Sodium hydroxide is a strong base and is incompatible with any compound that readily undergoes hydrolysis or oxidation. It will react with acids, esters, and ethers, especially in aqueous solution.

13 Method of Manufacture

Sodium hydroxide is manufactured by electrolysis of brine using inert electrodes. Chlorine is evolved as a gas at the anode and hydrogen is evolved as a gas at the cathode. The removal of chloride and hydrogen ions leaves sodium and hydroxide ions in solution. The solution is dried to produce the solid sodium hydroxide.

A second method uses the Kellner–Solvay cell. Saturated sodium chloride solution is electrolyzed between a carbon anode and a flowing mercury cathode. In this case the sodium is produced at the cathode rather than the hydrogen because of the readiness of sodium to dissolve in the mercury. The sodium–mercury amalgam is then exposed to water and a sodium hydroxide solution is produced.

14 Safety

Sodium hydroxide is widely used in the pharmaceutical and food industries and is generally regarded as a nontoxic material at low concentrations. At high concentrations it is a corrosive irritant to the skin, eyes, and mucous membranes.

LD_{50} (mouse, IP): 0.04 g/kg(2)
LD_{50} (rabbit, oral): 0.5 g/kg

15 Handling Precautions

Observe normal handling precautions appropriate to the quantity and concentration of material handled. Gloves, eye protection, a respirator, and other protective clothing should be worn.

Sodium hydroxide is a corrosive irritant to the skin, eyes, and mucous membranes. The solid and solutions cause burns, often with deep ulceration. It is moderately toxic on ingestion and harmful on inhalation.

In the UK, the occupational exposure limit for sodium hydroxide has been set at 2 mg/m^3 short-term.(3)

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (dental preparations; injections; inhalations; nasal, ophthalmic, oral, otic, rectal, topical, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Potassium hydroxide.

18 Comments

Sodium hydroxide is most commonly used in solutions of fixed concentration. Sodium hydroxide has some antibacterial and antiviral properties and is used as a disinfectant in some applications.(4–6) A specification for sodium hydroxide is contained in the Food Chemicals Codex (FCC).

The EINECS number for sodium hydroxide is 215-185-5.

19 Specific References

1 Zhan X, Yin G, Ma B. Improved stability of 25% vitamin C parenteral formulation. *Int J Pharm* 1998; **173**: 43–49.
2 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 3254–3255.
3 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*, Sudbury: Health and Safety Executive, 2002.
4 Brown P, Rohmer RG, Gajduseck DC. Sodium hydroxide decontamination of Creutzfeldt–Jakob disease virus. *N Engl J Med* 1984; **320**: 727.
5 Gasser G. Creutzfeldt–Jakob disease [letter]. *Br Med J* 1990; **300**: 1523.
6 Perkowski CA. Operational aspects of bioreactor contamination control. *J Parenter Sci Technol* 1990; **44**: 113–117.

20 General References

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21 Authors

AH Kibbe.

22 Date of Revision

12 August 2005.

Sodium Lactate

1 Nonproprietary Names

BP: Sodium lactate solution
PhEur: Natrii lactatis solutio
USP: Sodium lactate solution

2 Synonyms

E325; 2-hydroxypropanoic acid monosodium salt; *Lacolin*; lactic acid monosodium salt; lactic acid sodium salt; sodium α-hydroxypropionate.

3 Chemical Name and CAS Registry Number

Sodium lactate [72-17-3]

4 Empirical Formula and Molecular Weight

$C_3H_5NaO_3$ 112.06

5 Structural Formula

The PhEur 2005 and USP 28 describe sodium lactate solution as a mixture of the enantiomers of sodium 2-hydroxypropanoate in approximately equal proportions.

6 Functional Category

Antimicrobial preservative; buffering agent; emulsifying agent; flavoring agent; humectant.

7 Applications in Pharmaceutical Formulation or Technology

Sodium lactate is widely used in cosmetics,(1,2) food products and pharmaceutical applications including parenteral and topical formulations.

Therapeutically, sodium lactate is used in infusions as a component of Ringer-lactate solution; as an alternative for sodium hydrogencarbonate in light acidosis; as a rehydrating agent; and as a carrier for electrolyte concentrates or medicines in perfusion/infusion solutions.

8 Description

Sodium lactate occurs as a clear, colorless, slightly syrupy liquid. It is odorless, or has a slight odor with a characteristic saline taste. It is hygroscopic.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium lactate.

Test	PhEur 2005	USP 28
Characters	+	—
Identification	+	+
Appearance of solution	+	—
pH	6.5–9.0	5.0–9.0
Reducing sugars and sucrose	+	+
Methanol	⩽50 ppm[a]	+
Chlorides	⩽50 ppm	⩽0.05%
Oxalates and phosphates	+	+
Sulfates	⩽100 ppm	+
Aluminum	⩽0.1 ppm[a]	—
Barium	+	—
Iron	⩽10 ppm	—
Heavy metals	⩽10 ppm	⩽0.001%
Bacterial endotoxins	+[b]	—
Assay	96.0–104.0%	98.0–102.0%

[a] If intended for use in the manufacture of parenteral dosage forms, hemodialysis, or hemofiltration solutions.

[b] If intended for use in the manufacture of parenteral dosage forms without a further appropriate procedure for the removal of bacterial endotoxins.

10 Typical Properties

Acidity/alkalinity: pH = 7 for an aqueous solution.
Boiling point: 112°C
Hygroscopicity: very hygroscopic.
Melting point: 17°C with decomposition at 140°C.
Solubility: miscible with ethanol (95%), and with water.
Specific gravity: 1.31–1.34

11 Stability and Storage Conditions

Sodium lactate should be stored in a well-closed container in a cool, dry, place. Sodium lactate is combustible and decomposes upon heating.

12 Incompatibilities

See Lactic Acid.

13 Method of Manufacture

See Lactic Acid.

14 Safety

Sodium lactate occurs naturally in the body and is involved in physiological processes. It is generally regarded as a relatively nontoxic and nonirritant material when used as an excipient. Low concentrations are well tolerated by skin and eye mucosa, although higher concentrations should be avoided.

LD_{50} (rat, IP): 2 g/kg(3)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium lactate may cause eye irritation. When heated to decomposition, sodium lactate emits toxic fumes of Na_2O.(3)

16 Regulatory Status

GRAS listed (not for infant formulas). Included in the FDA Inactive Ingredient Guide (epidural, IM, IV, and SC injections; oral suspensions; topical gels and solutions). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Lactic Acid.

18 Comments

Generally, the commercially available product is a mixture with water containing 70–80% sodium lactate. The EINECS number for sodium lactate is 200-772-0.

19 Specific References

1 Suomela A, Kristoffersson E. Dry skin and moisturizing agents. *Acta Pharm Fenn* 1983; **92**(2): 67–76.
2 Middleton JD. Sodium lactate as a moisturizer. Cosmet Toiletries 1978; 93(Mar): 85–86.
3 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 2197–2198.

20 General References

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21 Authors

HJ de Jong.

22 Date of Revision

17 August 2005.

Sodium Lauryl Sulfate

1 Nonproprietary Names

BP: Sodium lauryl sulfate
JP: Sodium lauryl sulfate
PhEur: Natrii laurilsulfas
USPNF: Sodium lauryl sulfate

2 Synonyms

Dodecyl sodium sulfate; *Elfan 240*; sodium dodecyl sulfate; sodium laurilsulfate; sodium monododecyl sulfate; sodium monolauryl sulfate; *Texapon K12P.*

3 Chemical Name and CAS Registry Number

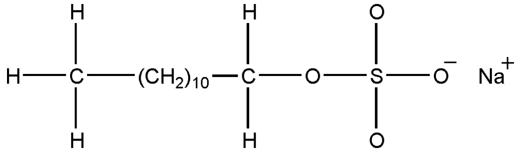
Sulfuric acid monododecyl ester sodium salt [151-21-3]

4 Empirical Formula and Molecular Weight

$C_{12}H_{25}NaO_4S$ 288.38

The USPNF 23 describes sodium lauryl sulfate as a mixture of sodium alkyl sulfates consisting chiefly of sodium lauryl sulfate ($C_{12}H_{25}NaO_4S$). The PhEur 2005 states that sodium lauryl sulfate should contain not less than 85% of sodium alkyl sulfates calculated as $C_{12}H_{25}NaO_4S$.

5 Structural Formula



$$H-\overset{H}{\underset{H}{C}}-(CH_2)_{10}-\overset{H}{\underset{H}{C}}-O-\overset{O}{\underset{O}{S}}-O^{-}\ Na^{+}$$

6 Functional Category

Anionic surfactant; detergent; emulsifying agent; skin penetrant; tablet and capsule lubricant; wetting agent.

7 Applications in Pharmaceutical Formulation or Technology

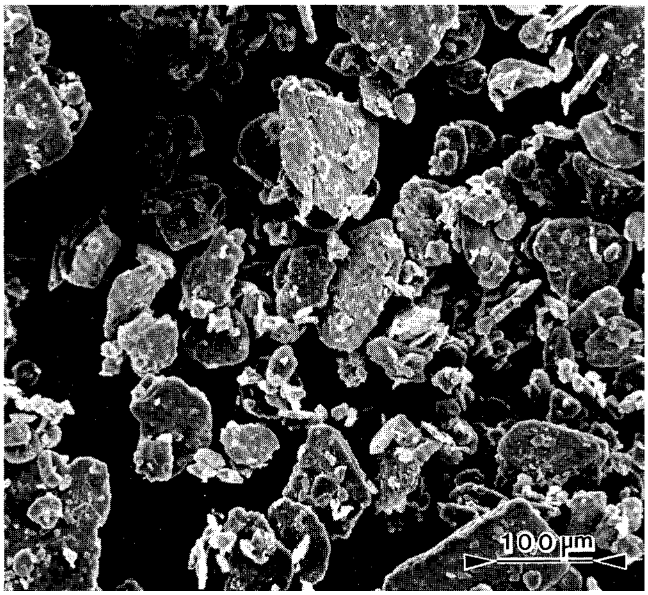
Sodium lauryl sulfate is an anionic surfactant employed in a wide range of nonparenteral pharmaceutical formulations and cosmetics; *see* Table I.

It is a detergent and wetting agent effective in both alkaline and acidic conditions. In recent years it has found application in analytical electrophoretic techniques: SDS (sodium dodecyl sulfate) polyacrylamide gel electrophoresis is one of the more widely used techniques for the analysis of proteins;(1) and sodium lauryl sulfate has been used to enhance the selectivity of micellar electrokinetic chromatography (MEKC).(2)

Table I: Uses of sodium lauryl sulfate.

Use	Concentration (%)
Anionic emulsifier, forms self-emulsifying bases with fatty alcohols	0.5–2.5
Detergent in medicated shampoos	≈10
Skin cleanser in topical applications	1
Solubilizer in concentrations greater than critical micelle concentration	>0.0025
Tablet lubricant	1.0–2.0
Wetting agent in dentrifices	1.0–2.0

SEM: 1
Excipient: Sodium lauryl sulfate
Manufacturer: Canadian Alcolac Ltd.
Magnification: 120×



8 Description

Sodium lauryl sulfate consists of white or cream to pale yellow-colored crystals, flakes, or powder having a smooth feel, a soapy, bitter taste, and a faint odor of fatty substances.

9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Acidity/alkalinity: pH = 7.0–9.5 (1% w/v aqueous solution)
Acid value: 0
Antimicrobial activity: sodium lauryl sulfate has some bacteriostatic action against Gram-positive bacteria but is

ineffective against many Gram-negative microorganisms. It potentiates the fungicidal activity of certain substances such as sulfanilamide and sulfathiazole.

Critical micelle concentration: 8.2 mmol/L (0.23 g/L) at 20°C

Density: 1.07 g/cm^3 at 20°C

HLB value: ≈ 40

Interfacial tension: 11.8 mN/m (11.8 dynes/cm) for a 0.05% w/v solution (unspecified nonaqueous liquid) at 30°C.

Melting point: 204–207°C (for pure substance)

Moisture content: $\leqslant 5\%$; sodium lauryl sulfate is not hygroscopic.

Solubility: freely soluble in water, giving an opalescent solution; practically insoluble in chloroform and ether.

Spreading coefficient: -7.0 (0.05% w/v aqueous solution) at 30°C

Surface tension: 25.2 mN/m (25.2 dynes/cm) for a 0.05% w/v aqueous solution at 30°C

Wetting time (Draize test): 118 seconds (0.05% w/v aqueous solution) at 30°C

SEM: 2
Excipient: Sodium lauryl sulfate
Manufacturer: Canadian Alcolac Ltd.
Magnification: 600×

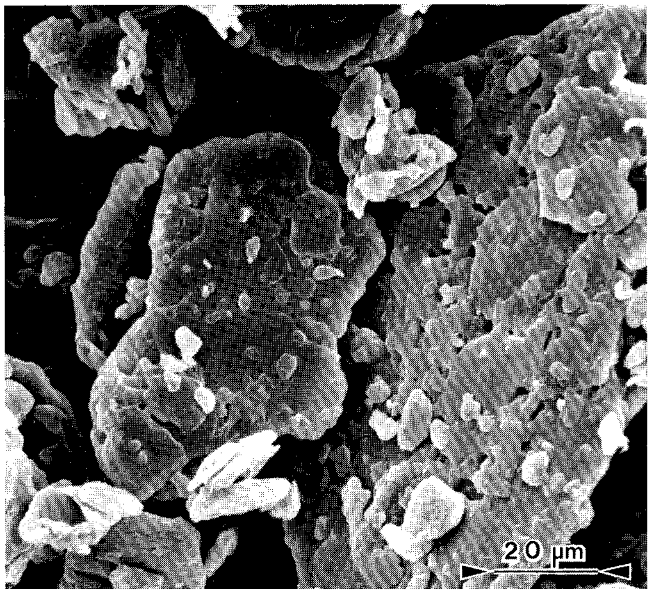


Table II: Pharmacopeial specifications for sodium lauryl sulfate.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Alkalinity	+	+	+
Heavy metals	—	—	$\leqslant 0.002\%$
Sodium chloride	$\leqslant 8.0\%$	+	+
Sodium sulfate	+	+	+
Unsulfated alcohols	$\leqslant 4.0\%$	—	$\leqslant 4.0\%$
Nonesterified alcohols	—	$\leqslant 4.0\%$	—
Total alcohols	$\geqslant 59.0\%$	—	$\geqslant 59.0\%$
Organic volatile impurities	—	—	+
Water	$\leqslant 5.0\%$	—	—
Assay (as $C_{12}H_{25}NaO_4S$)	—	$\geqslant 85.0\%$	—

11 Stability and Storage Conditions

Sodium lauryl sulfate is stable under normal storage conditions. However, in solution, under extreme conditions, i.e., pH 2.5 or below, it undergoes hydrolysis to lauryl alcohol and sodium bisulfate.

The bulk material should be stored in a well-closed container away from strong oxidizing agents in a cool, dry place.

12 Incompatibilities

Sodium lauryl sulfate reacts with cationic surfactants, causing loss of activity even in concentrations too low to cause precipitation. Unlike soaps, it is compatible with dilute acids and calcium and magnesium ions.

Solutions of sodium lauryl sulfate (pH 9.5–10.0) are mildly corrosive to mild steel, copper, brass, bronze, and aluminum. Sodium lauryl sulfate is also incompatible with some alkaloidal salts and precipitates with lead and potassium salts.

13 Method of Manufacture

Sodium lauryl sulfate is prepared by sulfation of lauryl alcohol, followed by neutralization with sodium carbonate.

14 Safety

Sodium lauryl sulfate is widely used in cosmetics and oral and topical pharmaceutical formulations. It is a moderately toxic material with acute toxic effects including irritation to the skin, eyes, mucous membranes, upper respiratory tract, and stomach. Repeated, prolonged exposure to dilute solutions may cause drying and cracking of the skin; contact dermatitis may develop.(3) Prolonged inhalation of sodium lauryl sulfate will damage the lungs. Pulmonary sensitization is possible, resulting in hyperactive airway dysfunction and pulmonary allergy. Animal studies have shown intravenous administration to cause marked toxic effects to the lung, kidney, and liver. Mutagenic testing in bacterial systems has proved negative.(4)

Adverse reactions to sodium lauryl sulfate in cosmetics and pharmaceutical formulations mainly concern reports of irritation to the skin(3,5–7) or eyes(8) following topical application.

Sodium lauryl sulfate should not be used in intravenous preparations for humans. The probable human lethal oral dose is 0.5–5.0 g/kg.

LD$_{50}$ (mouse, IP): 0.25 g/kg(9)
LD$_{50}$ (mouse, IV): 0.12 g/kg
LD$_{50}$ (rat, oral): 1.29 g/kg
LD$_{50}$ (rat, IP): 0.21 g/kg
LD$_{50}$ (rat, IV): 0.12 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Inhalation and contact with the skin and eyes should be avoided; eye protection, gloves, and other protective clothing, depending on the circumstances, are recommended. Adequate ventilation should be provided or a dust respirator should be worn. Prolonged or repeated exposure should be avoided. Sodium lauryl sulfate emits toxic fumes on combustion.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (dental preparations; oral capsules, suspensions, and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Cetostearyl alcohol; cetyl alcohol; magnesium lauryl sulfate; wax, anionic emulsifying.

Magnesium lauryl sulfate

Empirical formula: $C_{12}H_{26}O_4S{\cdot}HMg$
CAS number: [3097-08-3]
Comments: a soluble tablet lubricant.(10) The EINECS number for magnesium lauryl sulfate is 221-450-6.

18 Comments

A specification for sodium lauryl sulfate is contained in the Food Chemicals Codex (FCC). The EINECS number for sodium lauryl sulfate is 205-788-1.

19 Specific References

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21 Authors

S Behn.

22 Date of Revision

15 August 2005.

Sodium Metabisulfite

1 Nonproprietary Names

BP: Sodium metabisulphite
JP: Sodium metabisulfite
PhEur: Natrii metabisulfis
USPNF: Sodium metabisulfite

2 Synonyms

Disodium disulfite; disodium pyrosulfite; disulfurous acid, disodium salt; E223; natrii disulfis; sodium acid sulfite; sodium pyrosulfite.

3 Chemical Name and CAS Registry Number

Sodium pyrosulfite [7681-57-4]

4 Empirical Formula and Molecular Weight

$Na_2S_2O_5$ 190.1

5 Structural Formula

$Na_2S_2O_5$

6 Functional Category

Antioxidant.

7 Applications in Pharmaceutical Formulation or Technology

Sodium metabisulfite is used as an antioxidant in oral, parenteral, and topical pharmaceutical formulations, at concentrations of 0.01–1.0% w/v. Primarily, sodium metabisulfite is used in acidic preparations; for alkaline preparations, sodium sulfite is usually preferred; *see* Section 18. Sodium metabisulfite also has some antimicrobial activity, which is greatest at acid pH, and may be used as a preservative in oral preparations such as syrups.

In the food industry and in wine production, sodium metabisulfite is similarly used as an antioxidant, antimicrobial preservative, and antibrowning agent. However, at concentrations above about 550 ppm it imparts a noticeable flavor to preparations.

Sodium metabisulfite usually contains small amounts of sodium sulfite and sodium sulfate.

8 Description

Sodium metabisulfite occurs as colorless, prismatic crystals or as a white to creamy-white crystalline powder that has the odor of sulfur dioxide and an acidic, saline taste. Sodium metabisulfite crystallizes from water as a hydrate containing seven water molecules.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium metabisulfite.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Appearance of solution	+	+	—
pH (5% w/v solution)	—	3.5–5.0	—
Chloride	—	—	⩽0.05%
Thiosulfate	+	+	⩽0.05%
Arsenic	⩽4 ppm	⩽5 ppm	⩽3 ppm
Heavy metals	⩽20 ppm	⩽20 ppm	⩽0.002%
Selenium	—	—	<0.005%
Iron	⩽20 ppm	⩽20 ppm	⩽0.002%
Assay (as $Na_2S_2O_5$)	—	95.0–100.5%	—
Assay (as SO_2)	—	—	65.0–67.4%

10 Typical Properties

Acidity/alkalinity: pH = 3.5–5.0 for a 5% w/v aqueous solution at 20°C.

Melting point: sodium metabisulfite melts with decomposition at less than 150°C.

Osmolarity: a 1.38% w/v aqueous solution is isoosmotic with serum.

Solubility: *see* Table II.

Table II: Solubility of sodium metabisulfite.

Solvent	Solubility at 20°C unless otherwise stated
Ethanol (95%)	Slightly soluble
Glycerin	Freely soluble
Water	1 in 1.9 1 in 1.2 at 100°C

11 Stability and Storage Conditions

On exposure to air and moisture, sodium metabisulfite is slowly oxidized to sodium sulfate with disintegration of the crystals.(1) Addition of strong acids to the solid liberates sulfur dioxide.

In water, sodium metabisulfite is immediately converted to sodium (Na^+) and bisulfite (HSO_3^-) ions. Aqueous sodium metabisulfite solutions also decompose in air, especially on heating. Solutions that are to be sterilized by autoclaving should be filled into containers in which the air has been replaced with an inert gas, such as nitrogen. The addition of dextrose to aqueous sodium metabisulfite solutions results in a decrease in the stability of the metabisulfite.(2)

The bulk material should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

Sodium metabisulfite reacts with sympathomimetics and other drugs that are *ortho-* or *para-*hydroxybenzyl alcohol derivatives to form sulfonic acid derivatives possessing little or no pharmacological activity. The most important drugs subject to this inactivation are epinephrine (adrenaline) and its derivatives.(3) In addition, sodium metabisulfite is incompatible with chloramphenicol owing to a more complex reaction;(3) it also inactivates cisplatin in solution.(4,5)

It is incompatible with phenylmercuric acetate when autoclaved in eye drop preparations.(6)

Sodium metabisulfite may react with the rubber caps of multidose vials, which should therefore be pretreated with sodium metabisulfite solution.(7)

13 Method of Manufacture

Sodium metabisulfite is prepared by saturating a solution of sodium hydroxide with sulfur dioxide and allowing crystallization to occur; hydrogen is passed through the solution to exclude air. Sodium metabisulfite may also be prepared by saturating a solution of sodium carbonate with sulfur dioxide and allowing crystallization to occur, or by thermally dehydrating sodium bisulfite.

14 Safety

Sodium metabisulfite is widely used as an antioxidant in oral, topical, and parenteral pharmaceutical formulations; it is also widely used in food products.

Although it is extensively used in a variety of preparations, sodium metabisulfite and other sulfites have been associated with a number of severe to fatal adverse reactions.(8–19) These are usually hypersensitivity-type reactions and include bronchospasm and anaphylaxis. Allergy to sulfite antioxidants is estimated to occur in 5–10% of asthmatics, although adverse reactions may also occur in nonasthmatics with no history of allergy.

Following oral ingestion, sodium metabisulfite is oxidized to sulfate and is excreted in urine. Ingestion may result in gastric irritation, owing to the liberation of sulfurous acid, while ingestion of large amounts of sodium metabisulfite can cause colic, diarrhea, circulatory disturbances, CNS depression, and death.

In Europe, the acceptable daily intake of sodium metabisulfite and other sulfites used in foodstuffs has been set at up to 3.5 mg/kg body-weight, calculated as sulfur dioxide (SO_2). The WHO has similarly also set an acceptable daily intake of sodium metabisulfite, and other sulfites, at up to 7.0 mg/kg body-weight, calculated as sulfur dioxide (SO_2).(20)

LD_{50} (rat, IV): 0.12 g/kg(21)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium metabisulfite may be irritant to the skin and eyes; eye protection and gloves are recommended. In the UK, the long-term (8-hour TWA) occupational exposure limit for sodium metabisulfite is 5 mg/m^3.(22)

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (epidural, inhalation; IM, and IV injections; ophthalmic solutions; oral preparations, rectal, topical, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Nonmedicinal Ingredients.

17 Related Substances

Potassium metabisulfite; sodium bisulfite; sodium sulfite.

Sodium bisulfite

Empirical formula: $NaHSO_3$
Molecular weight: 104.07
CAS number: [7631-90-5]
Synonyms: E222; sodium hydrogen sulfite.
Appearance: white crystalline powder.
Density: 1.48 g/cm^3
Solubility: soluble 1 in 3.5 parts of water at 20°C; 1 in 2 parts of water at 100°C; and 1 in 70 parts of ethanol (95%).
Comments: most substances sold as sodium bisulfite contain significant, variable, amounts of sodium metabisulfite, as the latter is less hygroscopic and more stable during storage and shipment. *See* Section 18.

18 Comments

Sodium metabisulfite is used as an antioxidant at low pH, sodium bisulfite at intermediate pH, and sodium sulfite at higher pH values. A specification for sodium metabisulfite is contained in the Food Chemicals Codex (FCC).

The EINECS number for sodium metabisulfite is 231-673-0.

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21 Authors

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22 Date of Revision

17 August 2005.

Sodium Phosphate, Dibasic

1 Nonproprietary Names

BP:	Anhydrous disodium hydrogen phosphate Disodium hydrogen phosphate Disodium hydrogen phosphate dodecahydrate
JP:	Dibasic sodium phosphate
PhEur:	Dinatrii phosphas anhydricus Dinatrii phosphas dihydricus Dinatrii phosphas dodecahydricus
USP:	Dibasic sodium phosphate

Note that the BP 2004 and PhEur 2005 contain three separate monographs for the anhydrous, the dihydrate, and the dodecahydrate; the JP 2001 contains one monograph for the dodecahydrate; and the USP 28 contains one monograph for the anhydrous, the monohydrate, the dihydrate, the heptahydrate, and the dodecahydrate. *See also* Section 8.

2 Synonyms

Disodium hydrogen phosphate; disodium phosphate; E339; phosphoric acid, disodium salt; secondary sodium phosphate; sodium orthophosphate.

3 Chemical Name and CAS Registry Number

Anhydrous dibasic sodium phosphate	[7558-79-4]
Dibasic sodium phosphate dihydrate	[10028-24-7]
Dibasic sodium phosphate dodecahydrate	[10039-32-4]
Dibasic sodium phosphate heptahydrate	[7782-85-6]
Dibasic sodium phosphate hydrate	[10140-65-5]
Dibasic sodium phosphate monohydrate	[118830-14-1]

4 Empirical Formula and Molecular Weight

Na_2HPO_4	141.96
$Na_2HPO_4\cdot H_2O$	159.94
$Na_2HPO_4\cdot 2H_2O$	177.98
$Na_2HPO_4\cdot 7H_2O$	268.03
$Na_2HPO_4\cdot 12H_2O$	358.08

5 Structural Formula

$Na_2HPO_4\cdot xH_2O$ where x = 0, 1, 2, 7, or 12.

6 Functional Category

Buffering agent; sequestering agent.

7 Applications in Pharmaceutical Formulation or Technology

Dibasic sodium phosphate is used in a wide variety of pharmaceutical formulations as a buffering agent and as a sequestering agent. Therapeutically, dibasic sodium phosphate is used as a mild laxative and in the treatment of hypophosphatemia.(1,2)

Dibasic sodium phosphate is also used in food products; for example as an emulsifier in processed cheese.

8 Description

The USP 28 states that dibasic sodium phosphate is dried or contains, 1, 2, 7, or 12 molecules of water of hydration.

Anhydrous dibasic sodium phosphate occurs as a white powder. The dihydrate occurs as white or almost white, odorless crystals. The heptahydrate occurs as colorless crystals or as a white granular or caked salt that effloresces in warm, dry air. The dodecahydrate occurs as strongly efflorescent, colorless or transparent crystals.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium phosphate, dibasic(a).

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	+	+	—
Appearance of solution	+	+	—
pH	9.0–9.4	—	—
Reducing substances	—	+	—
Insoluble substances	—	—	⩽0.4%
Monosodium phosphate	—	⩽0.025	—
Carbonate	+	—	—
Chloride	⩽0.014%	+	⩽0.06%
Anhydrous	—	⩽200 ppm	—
Dihydrate	—	⩽400 ppm	—
Dodecahydrate	—	⩽200 ppm	—
Water	—	+	—
Anhydrous	—	—	—
Dihydrate	—	—	—
Dodecahydrate	—	57.0–61.0%	—
Sulfates	⩽0.038%	+	⩽0.2%
Anhydrous	—	⩽500 ppm	—
Dihydrate	—	⩽0.1%	—
Dodecahydrate	—	⩽500 ppm	—
Arsenic	⩽2 ppm	+	⩽16 ppm
Anhydrous	—	⩽2 ppm	—
Dihydrate	—	⩽4 ppm	—
Dodecahydrate	—	⩽2 ppm	—
Heavy metals	⩽10 ppm	+	⩽0.002%
Anhydrous	—	⩽10 ppm	—
Dihydrate	—	⩽20 ppm	—
Dodecahydrate	—	⩽10 ppm	—
Iron	—	+	—
Anhydrous	—	⩽20 ppm	—
Dihydrate	—	⩽40 ppm	—
Dodecahydrate	—	⩽20 ppm	—
Loss on drying	57.0–61.0%	+	+
Anhydrous	—	⩽1.0%	⩽5.0%
Monohydrate	—	—	10.3–12.0%
Dihydrate	—	19.5–21.0%	18.5–21.5%
Heptahydrate	—	—	43.0–50.0%
Dodecahydrate	—	—	55.0–64.0%
Assay (dried basis)	⩾98.0%	98.0–101.0%	98.0–100.5%

(a) PhEur 2005 (Suppl. 5.1) for the dodecahydrate.

10 Typical Properties

Acidity/alkalinity: pH = 9.1 for a 1% w/v aqueous solution of the anhydrous material at 25°C. A saturated aqueous solution of the dodecahydrate has a pH of about 9.5.

Ionization constants:

$pK_{a1} = 2.15$ at 25°C;[3]

$pK_{a2} = 7.20$ at 25°C;

$pK_{a3} = 12.38$ at 25°C.

Moisture content: the anhydrous form is hygroscopic and will absorb water on exposure to air, whereas the heptahydrate is stable in air.

Osmolarity: a 2.23% w/v aqueous solution of the dihydrate is isoosmotic with serum; a 4.45% w/v aqueous solution of the dodecahydrate is isoosmotic with serum.

Solubility: very soluble in water, more so in hot or boiling water; practically insoluble in ethanol (95%). The anhydrous material is soluble 1 in 8 parts of water, the heptahydrate 1 in 4 parts of water, and the dodecahydrate 1 in 3 parts of water.

11 Stability and Storage Conditions

The anhydrous form of dibasic sodium phosphate is hygroscopic. When heated to 40°C, the dodecahydrate fuses; at 100°C it loses its water of crystallization; and at a dull-red heat (about 240°C) it is converted into the pyrophosphate, $Na_4P_2O_7$. Aqueous solutions of dibasic sodium phosphate are stable and may be sterilized by autoclaving.

The bulk material should be stored in an airtight container, in a cool, dry place.

12 Incompatibilities

Dibasic sodium phosphate is incompatible with alkaloids, antipyrine, chloral hydrate, lead acetate, pyrogallol, resorcinol and calcium gluconate, and ciprofloxacin.[4] Interaction between calcium and phosphate, leading to the formation of insoluble calcium–phosphate precipitates, is possible in parenteral admixtures.

13 Method of Manufacture

Either bone phosphate (bone ash), obtained by heating bones to whiteness, or the mineral phosphorite is used as a source of tribasic calcium phosphate, which is the starting material in the industrial production of dibasic sodium phosphate.

Tribasic calcium phosphate is finely ground and digested with sulfuric acid. This mixture is then leached with hot water and neutralized with sodium carbonate, and dibasic sodium phosphate is crystallized from the filtrate.

14 Safety

Dibasic sodium phosphate is widely used as an excipient in parenteral, oral, and topical pharmaceutical formulations.

Phosphate occurs extensively in the body and is involved in many physiological processes since it is the principal anion of intracellular fluid. Most foods contain adequate amounts of phosphate, making hypophosphatemia (phosphate deficiency)[1] virtually unknown except for certain disease states[2] or in patients receiving total parenteral nutrition. Treatment is usually by the oral administration of up to 100 mmol of phosphate daily.

Approximately two-thirds of ingested phosphate is absorbed from the gastrointestinal tract, virtually all of it being excreted in the urine, and the remainder is excreted in the feces.

Excessive administration of phosphate, particularly intravenously, rectally, or in patients with renal failure, can cause hyperphosphatemia that may lead to hypocalcemia or other severe electrolyte imbalances.[5,6] Adverse effects occur less frequently following oral consumption, although phosphates act as mild saline laxatives when administered orally or rectally. Consequently, gastrointestinal disturbances including diarrhea, nausea, and vomiting may occur following the use of dibasic sodium phosphate as an excipient in oral formulations. However, the level of dibasic sodium phosphate used as an excipient in a pharmaceutical formulation is not usually associated with adverse effects.

LD_{50} (rat, oral): 17 g/kg[7]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Dibasic sodium phosphate may be irritating to the skin, eyes, and mucous membranes. Eye protection and gloves are recommended.

16 Regulatory Status

GRAS listed. Accepted in Europe for use as a food additive. Included in the FDA Inactive Ingredients Guide (injections; infusions; nasal, ophthalmic, oral, otic, topical, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Dibasic potassium phosphate; sodium phosphate, monobasic; tribasic sodium phosphate.

Dibasic potassium phosphate

Empirical formula: K_2HPO_4

Molecular weight: 174.15

CAS number: [7758-11-4]

Synonyms: dipotassium hydrogen orthophosphate; dipotassium hydrogen phosphate; dipotassium phosphate; E340; potassium phosphate.

Appearance: colorless or white, granular, hygroscopic powder.

Acidity/alkalinity: pH = 8.5–9.6 for a 5% w/v aqueous solution at 25°C.

Osmolarity: a 2.08% w/v aqueous solution of dibasic potassium phosphate is isoosmotic with serum.

Solubility: freely soluble in water; very slightly soluble in ethanol (95%).

Comments: one gram of dibasic potassium phosphate contains approximately 11.5 mmol of potassium and 5.7 mmol of phosphate.

Tribasic sodium phosphate

Empirical formula: $Na_3PO_4{\cdot}xH_2O$

Molecular weight: 163.94 for the anhydrous material

380.06 for the dodecahydrate ($12H_2O$)

CAS number: [7601-54-9] for the anhydrous material.

Synonyms: E339; trisodium orthophosphate; trisodium phosphate; TSP.

Acidity/alkalinity: pH = 12.1 for a 1% w/v aqueous solution of the anhydrous material at 25°C. A 1% w/v aqueous solution of the dodecahydrate at 25°C has a pH of 12.0–12.2.

Density:

1.3 g/cm^3 for the anhydrous material;
0.9 g/cm^3 for the dodecahydrate.

Solubility: the anhydrous material is soluble 1 in 8 parts of water, while the dodecahydrate is soluble 1 in 5 parts of water at 20°C.

18 Comments

One gram of anhydrous dibasic sodium phosphate represents approximately 14.1 mmol of sodium and 7.0 mmol of phosphate.

One gram of dibasic sodium phosphate dihydrate represents approximately 11.2 mmol of sodium and 5.6 mmol of phosphate.

One gram of dibasic sodium phosphate heptahydrate represents approximately 7.5 mmol of sodium and 3.7 mmol of phosphate.

One gram of dibasic sodium phosphate dodecahydrate represents approximately 5.6 mmol of sodium and 2.8 mmol of phosphate.

A specification for sodium phosphate, dibasic is contained in the Food Chemicals Codex (FCC).

19 Specific References

1 Lloyd CW, Johnson CE. Management of hypophosphatemia. *Clin Pharm* 1988; **7**: 123–128.
2 Holland PC, Wilkinson AR, Diez J, Lindsell DRM. Prenatal deficiency of phosphate, phosphate supplementation, and rickets in very-low-birthweight infants. *Lancet* 1990; **335**: 697–701.
3 Albert A, Serjearnt EP. *Ionization Constants of Acids and Bases*, 2nd edn. Edinburgh: Chapman and Hall, 1971.
4 Benjamin BE. Ciprofloxacin and sodium phosphates not compatible during actual Y-site injection [letter]. *Am J Health Syst Pharm* 1996; **53**: 1850–1851.
5 Haskell LP. Hypocalcaemic tetany induced by hypertonic-phosphate enema [letter]. *Lancet* 1985; **ii**: 1433.
6 Martin RR, Lisehora GR, Braxton M, Barcia PJ. Fatal poisoning from sodium phosphate enema: case report and experimental study. *J Am Med Assoc* 1987; **257**: 2190–2192.
7 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 3273.

20 General References

Sweetman SC, ed. *Martindale: The Complete Drug Reference*, 34th edn. London: Pharmaceutical Press, 2005: 1231.

21 Authors

AS Kearney.

22 Date of Revision

20 August 2005.

Sodium Phosphate, Monobasic

1 Nonproprietary Names

BP:	Anhydrous sodium dihydrogen phosphate Sodium dihydrogen phosphate monohydrate Sodium dihydrogen phosphate dihydrate
PhEur:	Natrii dihydrogenophosphas dihydricus
USP:	Monobasic sodium phosphate

Note that the BP 2004 contains three separate monographs for the anhydrous, the monohydrate, and the dihydrate; the PhEur 2005 contains a single monograph for the dihydrate; and the USP 28 contains one monograph for the anhydrous, the monohydrate and the dihydrate. *See also* Section 8.

2 Synonyms

Acid sodium phosphate; E339; *Kalipol 32*; monosodium orthophosphate; monosodium phosphate; phosphoric acid, monosodium salt; primary sodium phosphate; sodium biphosphate; sodium dihydrogen orthophosphate; sodium dihydrogen phosphate.

3 Chemical Name and CAS Registry Number

Anhydrous monobasic sodium phosphate	[7558-80-7]
Monobasic sodium phosphate monohydrate	[10049-21-5]
Monobasic sodium phosphate dihydrate	[13472-35-0]

4 Empirical Formula and Molecular Weight

NaH_2PO_4	119.98
$NaH_2PO_4{\cdot}H_2O$	137.99
$NaH_2PO_4{\cdot}2H_2O$	156.01

5 Structural Formula

$NaH_2PO_4{\cdot}xH_2O$ where $x = 0, 1$, or 2.

6 Functional Category

Buffering agent; emulsifying agent; sequestering agent.

7 Applications in Pharmaceutical Formulation or Technology

Monobasic sodium phosphate is used in a wide variety of pharmaceutical formulations as a buffering agent and as a sequestering agent. Therapeutically, monobasic sodium phosphate is used as a mild saline laxative and in the treatment of hypophosphatemia.(1–3)

Monobasic sodium phosphate is also used in food products, for example, in baking powders, and as a dry acidulant and sequestrant.

8 Description

The USP 28 states that monobasic sodium phosphate contains one or two molecules of water of hydration or is anhydrous.

The hydrated forms of monobasic sodium phosphate occur as odorless, colorless or white, slightly deliquescent crystals. The anhydrous form occurs as a white crystalline powder or granules.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium phosphate, monobasic.

Test	PhEur 2005	USP 28
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Aluminum, calcium and related elements	—	+
Arsenic	$\leqslant 2$ ppm	$\leqslant 8$ ppm
Chloride	$\leqslant 200$ ppm	$\leqslant 0.014\%$
Insoluble substances	—	$\leqslant 0.2\%$
Heavy metals	$\leqslant 10$ ppm	$\leqslant 0.002\%$
Insoluble substances	—	$\leqslant 0.2\%$
Iron	$\leqslant 10$ ppm	—
Organic volatile impurities	—	+
pH	4.2–4.5	4.1–4.5
Reducing substances	+	—
Sulfate	$\leqslant 300$ ppm	$\leqslant 0.15\%$
Water	+	+
Anhydrous	—	$\leqslant 2.0\%$
Monohydrate	—	10.0–15.0%
Dihydrate	21.5–24.0%	18.0–26.5%
Assay (dried basis)	98.0–100.5%	98.0–103.0%

10 Typical Properties

Acidity/alkalinity: pH = 4.1–4.5 for a 5% w/v aqueous solution of the monohydrate at 25°C.

Density: 1.915 g/cm^3 for the dihydrate.

Dissociation constant: $pK_a = 2.15$ at 25°C

Solubility: soluble 1 in 1 of water; very slightly soluble in ethanol (95%).

11 Stability and Storage Conditions

Monobasic sodium phosphate is chemically stable, although it is slightly deliquescent. On heating at 100°C, the dihydrate loses all of its water of crystallization. On further heating, it melts with decomposition at 205°C, forming sodium hydrogen pyrophosphate, $Na_2H_2P_2O_7$. At 250°C it leaves a final residue of sodium metaphosphate, $NaPO_3$.

Aqueous solutions are stable and may be sterilized by autoclaving.

Monobasic sodium phosphate should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Monobasic sodium phosphate is an acid salt and is therefore generally incompatible with alkaline materials and carbonates; aqueous solutions of monobasic sodium phosphate are acidic and will cause carbonates to effervesce.

Monobasic sodium phosphate should not be administered concomitantly with aluminum, calcium, or magnesium salts since they bind phosphate and could impair its absorption from the gastrointestinal tract. Interaction between calcium and phosphate, leading to the formation of insoluble calcium phosphate precipitates, is possible in parenteral admixtures.(4–6)

13 Method of Manufacture

Monobasic sodium phosphate is prepared by adding phosphoric acid to a hot, concentrated solution of disodium phosphate until the liquid ceases to form a precipitate with barium chloride. This solution is then concentrated and the monobasic sodium phosphate is crystallized.

14 Safety

Monobasic sodium phosphate is widely used as an excipient in parenteral, oral, and topical pharmaceutical formulations.

Phosphate occurs extensively in the body and is involved in many physiological processes since it is the principal anion of intracellular fluid. Most foods contain adequate amounts of phosphate, making hypophosphatemia(1) virtually unknown except for in certain disease states(2) or in patients receiving total parenteral nutrition. Treatment is usually by the oral administration of up to 100 mmol of phosphate daily.

Approximately two-thirds of ingested phosphate is absorbed from the gastrointestinal tract, virtually all of it being excreted in the urine, and the remainder is excreted in the feces.

Excessive administration of phosphate, particularly intravenously, rectally, or in patients with renal failure, can cause hyperphosphatemia that may lead to hypocalcemia or other severe electrolyte imbalances.(7–9) Adverse effects occur less frequently following oral consumption, although phosphates act as mild saline laxatives when administered orally or rectally (2–4 g of monobasic sodium phosphate in an aqueous solution is used as a laxative). Consequently, gastrointestinal disturbances including diarrhea, nausea, and vomiting may occur following the use of monobasic sodium phosphate as an excipient in oral formulations. However, the level of monobasic sodium phosphate used as an excipient in a pharmaceutical formulation is not usually associated with adverse effects.

LD_{50} (rat, IM): 0.25 g/kg(10)
LD_{50} (rat, oral): 8.29 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Monobasic sodium phosphate may be irritant to the skin, eyes, and mucous membranes. Eye protection and gloves are recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (injections; infusions; ophthalmic, oral, topical, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Dibasic sodium phosphate; monobasic potassium phosphate.

Monobasic potassium phosphate

Empirical formula: KH_2PO_4
Molecular weight: 136.09
CAS number: [7778-77-0]
Synonyms: E340; monopotassium phosphate; potassium acid phosphate; potassium biphosphate; potassium dihydrogen orthophosphate.
Appearance: colorless crystals or a white, odorless, granular or crystalline powder.
Acidity/alkalinity: pH $\approx$ 4.5 for a 1% w/v aqueous solution at 25°C.
Solubility: freely soluble in water; practically insoluble in ethanol (95%).
Comments: 1 g of monobasic potassium phosphate represents approximately 7.3 mmol of potassium and of phosphate.

The EINECS number for monobasic potassium phosphate is 231-913-4.

18 Comments

One gram of anhydrous monobasic sodium phosphate represents approximately 8.3 mmol of sodium and of phosphate.

One gram of monobasic sodium phosphate monohydrate represents approximately 7.2 mmol of sodium and of phosphate.

One gram of monobasic sodium phosphate dihydrate represents approximately 6.4 mmol of sodium and of phosphate.

A specification for sodium phosphate monobasic is contained in the Food Chemicals Codex (FCC). The EINECS number for monobasic sodium phosphate is 231-449-2.

19 Specific References

1 Lloyd CW, Johnson CE. Management of hypophosphatemia. *Clin Pharm* 1988; **7**: 123–128.
2 Holland PC, Wilkinson AR, Diez J, Lindsell DRM. Prenatal deficiency of phosphate, phosphate supplementation, and rickets in very-low-birthweight infants. *Lancet* 1990; **335**: 697–701.
3 Rosen GH, Boullata JI, O'Rangers EA, *et al*. Intravenous phosphate repletion regimen for critically ill patients with moderate hypophosphatemia. *Crit Care Med* 1995; **23**: 1204–1210.
4 Eggert LD, Rusho WJ, Mackay MW, Chan GM. Calcium and phosphorus compatibility in parenteral nutrition solutions for neonates. *Am J Hosp Pharm* 1982; **39**: 49–53.
5 Niemiec PW, Vanderveen TW. Compatibility considerations in parenteral nutrient solutions. *Am J Hosp Pharm* 1984; **41**: 893–911.
6 Pereira-da-Silva L, Nurmamodo A, Amaral JM, *et al*. Compatibility of calcium and phosphate in four parenteral nutrition solutions for preterm neonates. *Am J Health Syst Pharm* 2003; **60**: 1041–1044.
7 Haskell LP. Hypocalcaemic tetany induced by hypertonic-phosphate enema [letter]. *Lancet* 1985; **ii**: 1433.
8 Larson JE, Swigart SA, Angle CR. Laxative phosphate poisoning: pharmacokinetics of serum phosphorus. *Hum Toxicol* 1986; **5**: 45–49.

9 Martin RR, Lisehora GR, Braxton M, Barcia PJ. Fatal poisoning from sodium phosphate enema: case report and experimental study. *J Am Med Assoc* 1987; **257**: 2190–2192.
10 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 3274.

20 General References

Sweetman SC, ed. *Martindale: The Complete Drug Reference*, 34th edn. London: Pharmaceutical Press, 2005: 1230.

21 Authors

LY Galichet.

22 Date of Revision

17 August 2005.

Sodium Propionate

1 Nonproprietary Names

PhEur: Natrii propionas
USPNF: Sodium propionate

2 Synonyms

E281; ethylformic acid, sodium salt, hydrate; methylacetic acid, sodium salt, hydrate; sodium propanoate hydrate; sodium propionate hydrate.

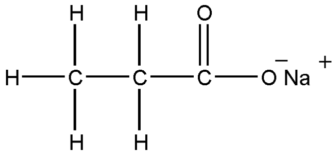
3 Chemical Name and CAS Registry Number

Propionic acid, sodium salt, hydrate [6700-17-0]
Propionic acid, sodium salt, anhydrous [137-40-6]

4 Empirical Formula and Molecular Weight

$C_3H_5NaO_2{\cdot}xH_2O$	114.06 (for monohydrate)
$C_3H_5NaO_2$	96.06 (for anhydrous)

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

As an excipient, sodium propionate is used in oral pharmaceutical formulations as an antimicrobial preservative. Like propionic acid, sodium propionate and other propionic acid salts are fungistatic and bacteriostatic against a number of Gram-positive cocci. Propionates are more active against molds than is sodium benzoate, but have essentially no activity against yeasts; *see* Section 10.

Therapeutically, sodium propionate has been used topically in concentrations up to 10% w/w alone or in combination with other propionates, caprylates, or other antifungal agents, in the form of ointments or solutions for the treatment of dermatophyte infections. Eye drops containing 5% w/v sodium propionate have also been used. *See* Section 18.

In food processes, particularly baking, sodium propionate is used as an antifungal agent; it may also be used as a flavoring agent in food products. In veterinary medicine, sodium propionate is used therapeutically as a glucogenic substance in ruminants.(1)

8 Description

Sodium propionate occurs as colorless transparent crystals or as a granular, free-flowing, crystalline powder. It is odorless, or with a slight characteristic odor, and is deliquescent in moist air. Sodium propionate has a characteristic, slightly cheeselike taste, although by itself it is unpalatable.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium propionate.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Alkalinity	—	+
pH	7.8–9.2	—
Water	—	⩽1.0%
Heavy metals	⩽10 ppm	⩽0.001%
Related substances	+	—
Readily oxidizable substances	+	—
Iron	⩽10 ppm	—
Organic volatile impurities	—	+
Loss on drying	0.50%	—
Assay (dried basis)	99.0–101.0%	99.0–100.5%

10 Typical Properties

Antimicrobial activity: sodium propionate, propionic acid, and other propionates possess mainly antifungal activity and are used as preservatives primarily against molds; they exhibit essentially no activity against yeasts. Although, in general, propionates exhibit little activity against bacteria, sodium propionate is effective against *Bacillus mesenterium*, the organism that causes 'rope' in bread. Antimicrobial activity is largely dependent upon the presence of the free acid and hence propionates exhibit optimum activity at acid pH, notably at less than pH 5. Synergistic effects occur between propionates and carbon dioxide or sorbic acid. *See also* Propionic acid.

Solubility: soluble 1 in 24 of ethanol (95%), 1 in 1 of water, and 1 in 0.65 of boiling water; practically insoluble in chloroform and ether.

11 Stability and Storage Conditions

Sodium propionate is deliquescent and should therefore be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Incompatibilities for sodium propionate are similar to those of other weak organic acids.

13 Method of Manufacture

Sodium propionate is prepared by the reaction of propionic acid with sodium carbonate or sodium hydroxide.

14 Safety

Sodium propionate and other propionates are used in oral pharmaceutical formulations, food products, and cosmetics. The free acid, propionic acid, occurs naturally at levels up to 1% w/w in certain cheeses.

Following oral consumption, propionate is metabolized in mammals in a manner similar to that of fatty acids. Toxicity studies in animals have shown sodium propionate and other propionates to be relatively nontoxic materials.(2,3) In veterinary medicine, sodium propionate is used as a therapeutic agent for cattle and sheep.(1)

In humans, 6 g of sodium propionate has been administered daily without harm.(2) However, allergic reactions to propionates can occur.

LD_{50} (mouse, oral): 6.33 g/kg(4)
LD_{50} (mouse, SC): 2.1 g/kg
LD_{50} (rabbit, skin): 1.64 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium propionate may be irritant to the eyes and skin. Gloves, eye protection, and a dust-mask are recommended. When heated to decomposition, sodium propionate emits toxic fumes of sodium monoxide, Na_2O.

In the UK, the occupational exposure limits for propionic acid are 31 mg/m^3 (10 ppm) long-term (8-hour TWA) and 46 mg/m^3 (15 ppm) short-term.(5)

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. In cheese products, propionates are limited to 0.3% w/w concentration; a limit of 0.32% w/w is applied in flour and white bread rolls, while a limit of 0.38% w/w is applied in whole wheat products.

Included in the FDA Inactive Ingredients Guide (oral capsules, powder, suspensions, and syrups). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Anhydrous sodium propionate; calcium propionate; potassium propionate; propionic acid; zinc propionate.

Anhydrous sodium propionate

Empirical formula: $C_3H_5O_2Na$
Molecular weight: 96.06
CAS number: [137-40-6]
Synonyms: E281; propanoic acid, sodium salt, anhydrous.
Safety:

LD_{50} (mouse, oral): 2.35 g/kg(4)
LD_{50} (rat, oral): 3.92 g/kg

Calcium propionate

Empirical formula: $C_6H_{10}O_4Ca$
Molecular weight: 186.22
CAS number: [4075-81-4]
Synonyms: calcium dipropionate; E282; propanoic acid, calcium salt; propionic acid, calcium salt.
Appearance: white crystalline powder.
Solubility: soluble in water; slightly soluble in ethanol (95%) and methanol; practically insoluble in acetone and benzene.
Method of manufacture: prepared by the reaction of propionic acid and calcium hydroxide.
Comments: occurs as the monohydrate or trihydrate.

Potassium propionate

Empirical formula: $C_3H_5O_2K$
Molecular weight: 112.17
CAS number: [327-62-8]
Synonyms: E283; propanoic acid, potassium salt; propionic acid, potassium salt.
Appearance: white crystalline powder.
Comments: occurs as the anhydrous form and the monohydrate. Decomposes in moist air to give off propionic acid.

Zinc propionate

Empirical formula: $C_6H_{10}O_4Zn$
Molecular weight: 211.52
CAS number: [557-28-8]
Synonyms: propanoic acid, zinc salt; propionic acid, zinc salt.
Appearance: white platelets or needlelike crystals (for the monohydrate).
Solubility: the anhydrous form is soluble 1 in 36 of ethanol (95%) at 15°C, 1 in 6 of boiling ethanol (95%), and 1 in 3 of water at 15°C.
Method of manufacture: prepared by dissolving zinc oxide in dilute propionic acid solution.
Comments: occurs as the anhydrous form and the monohydrate. Decomposes in moist air to give off propionic acid.

18 Comments

Propionates are used as antimicrobial preservatives in preference to propionic acid since they are less corrosive.

The therapeutic use of sodium propionate in topical antifungal preparations has largely been superseded by a new generation of antifungal drugs. A specification for sodium propionate is contained in the Food Chemicals Codex (FCC). The EINECS number for sodium propionate is 205-290-4.

19 Specific References

1 Bishop Y, ed. *The Veterinary Formulary*, 6th edn. London: Pharmaceutical Press, 2005: 419–420.
2 Heseltine WW. A note on sodium propionate. *J Pharm Pharmacol* 1952; **4**: 120–122.
3 Graham WD, Teed H, Grice HC. Chronic toxicity of bread additives to rats. *J Pharm Pharmacol* 1954; **6**: 534–545.
4 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 3276.
5 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.

20 General References

Doores S. Organic acids. In: Branen AL, Davidson PM, eds. *Antimicrobials in Foods*. New York: Marcel Dekker, 1983: 85–87.
Furia TE, ed. *CRC Handbook of Food Additives*. Cleveland, OH: CRC Press, 1972: 137–141.

21 Authors

SC Owen.

22 Date of Revision

9 August 2005.

Sodium Starch Glycolate

1 Nonproprietary Names

BP: Sodium starch glycollate
PhEur:Carboxymethylamylum natricum
USPNF: Sodium starch glycolate

2 Synonyms

Carboxymethyl starch, sodium salt; *Explosol*; *Explotab*; *Glycolys*; *Primojel*; starch carboxymethyl ether, sodium salt; *Tablo*; *Vivastar P.*

3 Chemical Name and CAS Registry Number

Sodium carboxymethyl starch [9063-38-1]

4 Empirical Formula and Molecular Weight

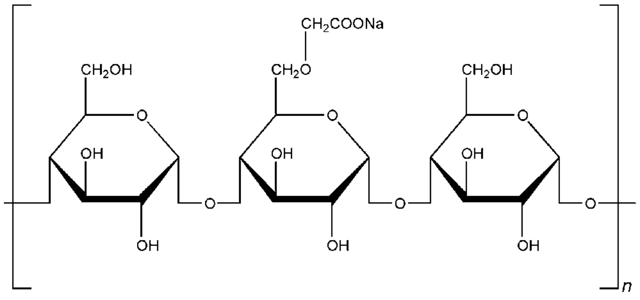
The USPNF 23 states that sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch, containing 2.8–4.2% sodium.

The PhEur 2005 describes three types of material: Types A and B occur as the sodium salt of a cross-linked partly *O*-carboxymethylated potato starch, containing 2.8–4.2% and 2.0–3.4% of sodium respectively. Type C is the sodium salt of a cross-linked by physical dehydration, partly *O*-carboxymethylated starch containing 2.8–5.0% sodium.

The JP, PhEur and USPNF monographs have been harmonised for Type A and Type B variants.

Sodium starch glycolate may be characterized by the degree of substitution and crosslinking. The molecular weight is typically 5×10^5–1×10^6.

5 Structural Formula



6 Functional Category

Tablet and capsule disintegrant.

7 Applications in Pharmaceutical Formulation or Technology

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule(1–6) and tablet formulations.(7–10) It is commonly used in tablets prepared by either direct-compression(11–13) or wet-granulation processes.(14–16) The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.(17–20)

Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time.(10–14)

Sodium starch glycolate has also been investigated for use as a suspending vehicle.(21,22)

8 Description

Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder. The PhEur 2005 states that it consists of oval or spherical granules, 30–100 μm in diameter, with some less-spherical granules ranging from 10–35 μm in diameter.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium starch glycolate.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Appearance of solution	+	—
pH	+	3.0–5.0 or 5.5–7.5
Type A	5.5–7.5	—
Type B	3.0–5.9	—
Type C	5.5–7.5	—
Heavy metals	⩽20 ppm	⩽0.002%
Iron	⩽20 ppm	⩽0.002%
Loss on drying	+	+
Type A	⩽10.0%	—
Type B	⩽10.0%	—
Type C	⩽7.0%	—
Microbial limits	+	+
Sodium chloride	+	+
Type A	⩽7.0%	⩽7.0%
Type B	⩽7.0%	⩽7.0%
Type C	⩽1.0%	—
Sodium glycolate	⩽2.0%	—
Assay (of Na)	+	2.8–4.2%
Type A	2.8–4.2%	—
Type B	2.0–3.4%	—
Type C	2.8–5.0%	—

10 Typical Properties

Acidity/alkalinity: pH = 3.0–5.0 or pH = 5.5–7.5 for a 3.3% w/v aqueous dispersion. *See* Section 18.

Ash: $\leqslant$15% for *Explotab*

Density (bulk): 0.756 g/cm^3;
0.75 g/cm^3 for *Explotab*;
0.81 g/cm^3 for *Primojel*;
0.67 g/cm^3 for *Tablo*.

Density (tapped): 0.945 g/cm^3;
0.88 g/cm^3 for *Explotab*;
0.98 g/cm^3 for *Primojel*;
0.83 g/cm^3 for *Tablo*.

Density (true): 1.443 g/cm^3;
1.51 g/cm^3 for *Explotab*;
1.56 g/cm^3 for *Primojel*;
1.49 g/cm^3 for *Tablo*.

Melting point: does not melt, but chars at approximately 200°C.

Particle size distribution: 100% of particles less than 106 μm in size. Average particle size is 35–55 μm for *Explotab*.

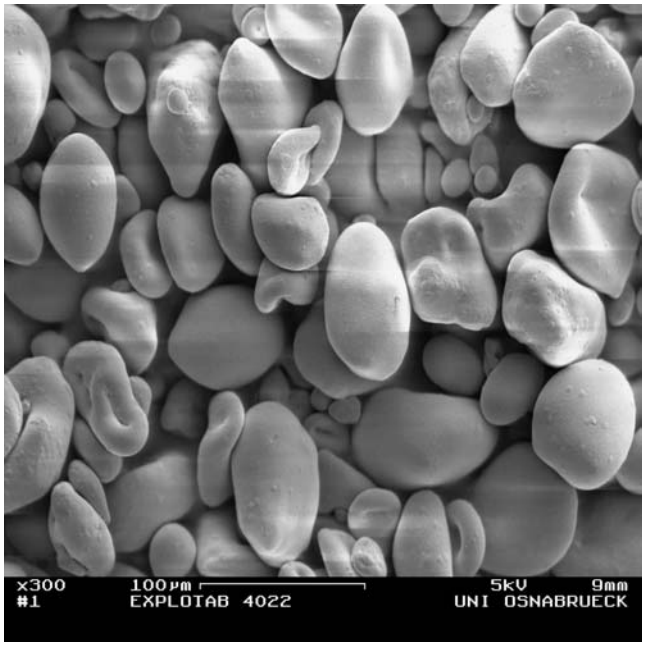
Solubility: sparingly soluble in ethanol (95%); practically insoluble in water. At a concentration of 2% w/v sodium starch glycolate disperses in cold water and settles in the form of a highly hydrated layer.

Specific surface area: 0.24 m^2/g;
0.202 m^2/g for *Explotab*;
0.185 m^2/g for *Primojel*;
0.335 m^2/g for *Tablo*;

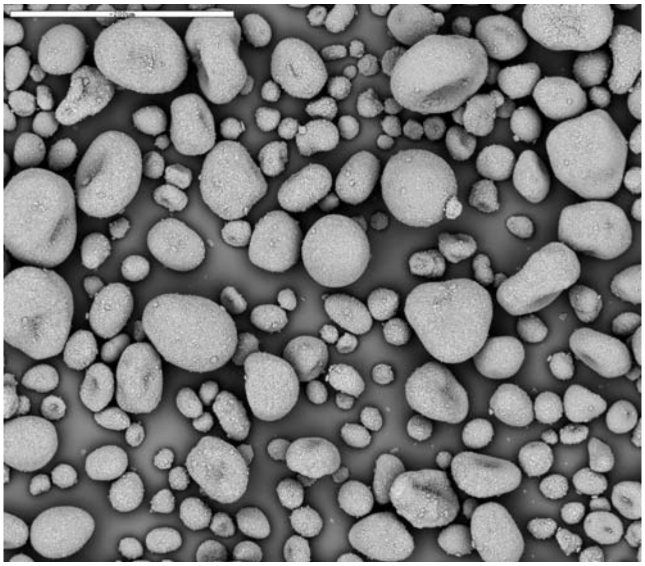
Swelling capacity: in water, sodium starch glycolate swells to up to 300 times its volume.

Viscosity (dynamic): $\leqslant$200 mPa s (200 cP) for a 4% w/v aqueous dispersion. Viscosity is 4.26 mPa s for a 2% w/v aqueous dispersion.

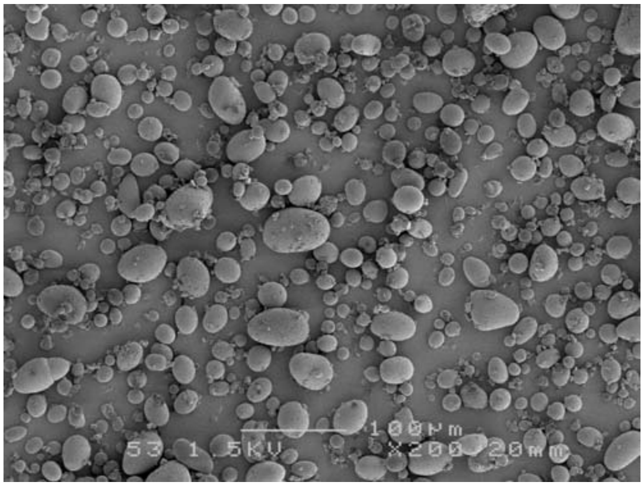
SEM 1
Excipient: Sodium starch glycolate (*Explotab*)
Manufacturer: JRS Pharma
Magnification: 300×
Voltage: 5 kV



SEM 2
Excipient: Sodium starch glycolate (*Glycolys*)
Manufacturer: Roquettes Frères



SEM 3
Excipient: Sodium starch glycolate (*Primojel*)
Manufacturer: DMV-International
Magnification: 200×
Voltage: 1.5 kV

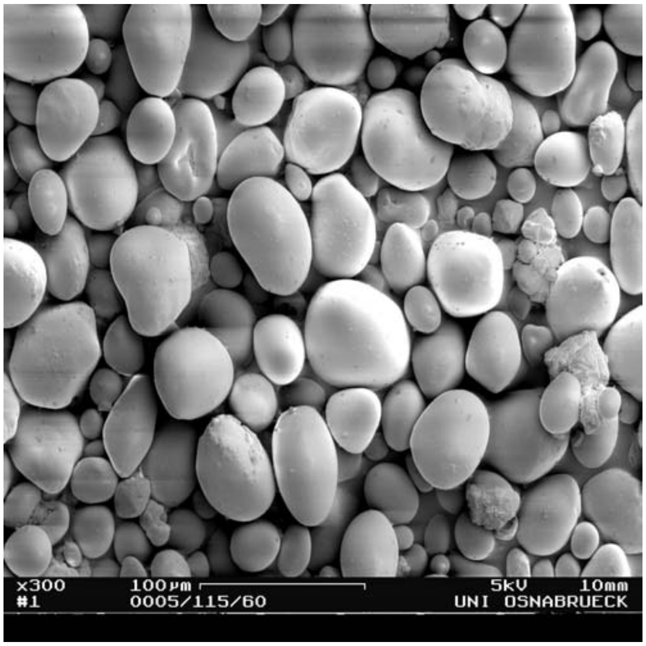


11 Stability and Storage Conditions

Tablets prepared with sodium starch glycolate have good storage properties.(23–25) Sodium starch glycolate is stable and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.

The physical properties of sodium starch glycolate remain unchanged for up to 3–5 years if it is stored at moderate temperatures and humidity.

SEM 4
Excipient: Sodium starch glycolate (*Vivastar P*)
Manufacturer: JRS Pharma
Magnification: 300×
Voltage: 5 kV



12 Incompatibilities

Sodium starch glycolate is incompatible with ascorbic acid.(26)

13 Method of Manufacture

Sodium starch glycolate is a substituted derivative of potato starch. Typically, commercial products are also cross-linked.

Starch is carboxymethylated by reacting it with sodium chloroacetate in an alkaline medium followed by neutralization with citric acid or some other acid. Crosslinking may be achieved either by physical methods or chemically by using reagents such as phosphorus oxytrichloride or sodium trimetaphosphate.(27)

14 Safety

Sodium starch glycolate is widely used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may be harmful.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium starch glycolate may be irritant to the eyes; eye protection and gloves are recommended. A dust mask or respirator is recommended for processes that generate a large quantity of dust.

16 Regulatory Acceptance

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Pregelatinized starch; starch.

18 Comments

The physical properties of sodium starch glycolate, and hence its effectiveness as a disintegrant, are affected by the degree of crosslinkage, extent of carboxymethylation, and purity.(28,29)

Sodium starch glycolate has been reported to interact with glycopeptide antibiotics,(30,31) basic drugs, and increase the photostability of norfloxacin.(32) The solubility of the formulation matrix and mode of incorporation in wet granulation can affect the disintegration time; disintegration times can be slower in tablets containing high levels of soluble excipients.(33)

Commercially, sodium starch glycolate is available in a number of speciality grades, e.g. low pH (*Explotab Low pH*, *Glycolys Low pH*); low viscosity (*Explotab CLV*, *Glycolys LV*); enhanced swelling (*Explotab V17*); low solvent (*Vivastar PSF*); and viscous (*Vivastar P3500*, *P5000*).

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21 Authors

S Edge, RW Miller.

22 Date of Revision

17 August 2005.

Sodium Stearyl Fumarate

1 Nonproprietary Names

BP: Sodium stearyl fumarate
PhEur: Natrii stearylis fumaras
USPNF: Sodium stearyl fumarate

2 Synonyms

Fumaric acid, octadecyl ester, sodium salt; *Pruv*; sodium monostearyl fumarate.

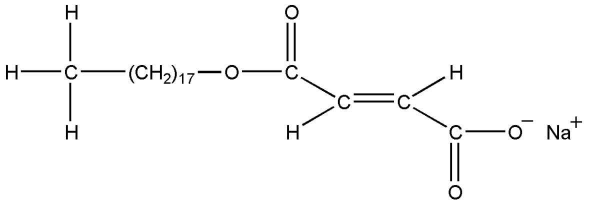
3 Chemical Name and CAS Registry Number

2-Butenedioic acid, monooctadecyl ester, sodium salt [4070-80-8]

4 Empirical Formula and Molecular Weight

$C_{22}H_{39}NaO_4$ 390.5

5 Structural Formula



6 Functional Category

Tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Sodium stearyl fumarate is used as a lubricant in capsule and tablet formulations at 0.5–2.0% w/w concentration.(1–9) It is also used in certain food applications; *see* Section 16.

8 Description

Sodium stearyl fumarate is a fine, white powder with agglomerates of flat, circular-shaped particles.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium stearyl fumarate.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Water	⩽5.0%	⩽5.0%
Lead	—	⩽0.001%
Heavy metals	—	⩽0.002%
Related substances	+	—
Sodium stearyl maleate	—	⩽0.25%
Stearyl alcohol	—	⩽0.5%
Saponification value (anhydrous basis)	—	142.2–146.0
Organic volatile impurities	—	+
Assay (anhydrous basis)	99.0–101.5%	99.0–101.5%

10 Typical Properties

Acidity/alkalinity: pH = 8.3 for a 5% w/v aqueous solution at 90°C.
Density: 1.107 g/cm^3
Density (bulk): 0.2–0.35 g/cm^3
Density (tapped): 0.3–0.5 g/cm^3
Melting point: 224–245°C (with decomposition)
Solubility: *see* Table II.

Table II: Solubility of sodium stearyl fumarate.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	Practically insoluble
Chloroform	Practically insoluble
Ethanol	Practically insoluble
Methanol	Slightly soluble
Water	1 in 20 000 at 25°C 1 in 10 at 80°C 1 in 5 at 90°C

Specific surface area: 1.2–2.0 m^2/g

11 Stability and Storage Conditions

At ambient temperature, sodium stearyl fumarate is stable for up to 3 years when stored in amber glass bottles with polyethylene screw caps.

The bulk material should be stored in a well-closed container in a cool, dry place.

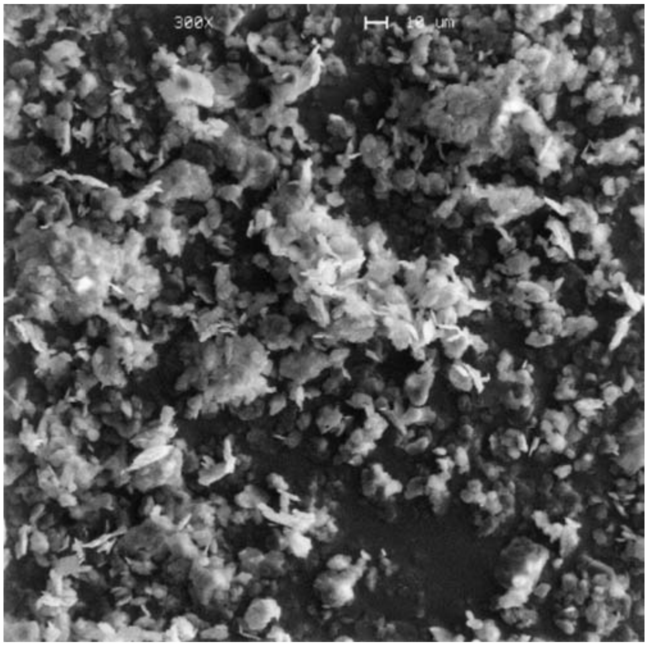
12 Incompatibilities

Sodium stearyl fumarate is reported to be incompatible with chlorhexidine acetate.(10)

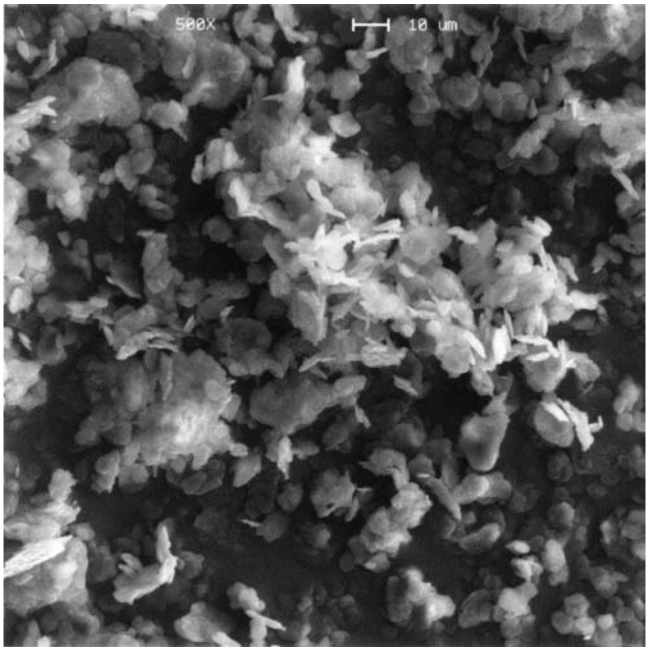
13 Method of Manufacture

Stearyl alcohol is reacted with maleic anhydride. The product of this reaction then undergoes an isomerization step followed by salt formation to produce sodium stearyl fumarate.

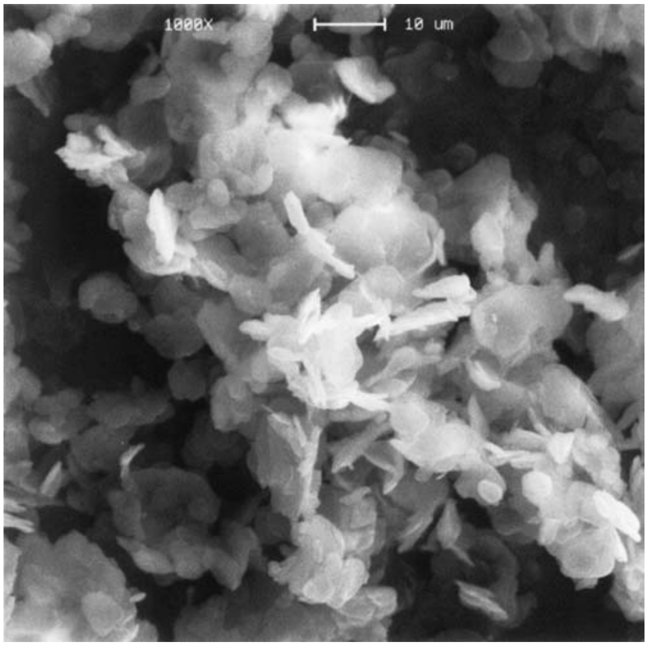
SEM: 1
Excipient: Sodium stearyl fumarate
Manufacturer: JRS Pharma LP
Lot No.: 255-01
Magnification: 300×



SEM: 2
Excipient: Sodium stearyl fumarate
Manufacturer: JRS Pharma LP
Lot No.: 255-01
Magnification: 500×



SEM: 3
Excipient: Sodium stearyl fumarate
Manufacturer: JRS Pharma LP
Lot No.: 255-01
Magnification: 1000×



14 Safety

Sodium stearyl fumarate is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material.

Metabolic studies of sodium stearyl fumarate in the rat and dog indicated that approximately 80% was absorbed and 35% was rapidly metabolized. The fraction absorbed was hydrolyzed to stearyl alcohol and fumaric acid, with the stearyl alcohol further oxidized to stearic acid. In the dog, sodium stearyl fumarate that was not absorbed was excreted unchanged in the feces within 24 hours.(11)

Stearyl alcohol and stearic acid are naturally occurring constituents in various food products, while fumaric acid is a normal constituent of body tissue. Stearates and stearyl citrate have been reviewed by the WHO and an acceptable daily intake for stearyl citrate has been set at up to 50 mg/kg bodyweight.(12) The establishment of an acceptable daily intake for stearates(12) and fumaric acid(13) was thought unnecessary.

Disodium fumarate has been reported to have a toxicity not greatly exceeding that of sodium chloride.(14,15)

See Fumaric Acid, Stearic Acid, and Stearyl Alcohol for further information.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium stearyl fumarate should be handled in a well-ventilated environment; eye protection is recommended.

16 Regulatory Status

GRAS listed. Permitted by the FDA for direct addition to food for human consumption as a conditioning or stabilizing agent in various bakery products, flour-thickened foods, dehydrated potatoes, and processed cereals up to 0.2–1.0% by weight of the food. Included in nonparenteral medicines licensed in the UK. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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18 Comments

Sodium stearyl fumarate is supplied in a pure form and is often of value when the less pure stearate-type lubricants are unsuitable owing to chemical incompatibility. Sodium stearyl fumarate is less hydrophobic than magnesium stearate or stearic acid and has a less retardant effect on tablet dissolution than magnesium stearate. A specification for sodium stearyl fumarate is contained in the Food Chemicals Codex (FCC).

The EINECS number for sodium stearyl fumarate is 203-743-0.

19 Specific References

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21 Authors

PJ Weller.

22 Date of Revision

19 April 2005.

Sodium Sulfite

1 Nonproprietary Names

BP: Sodium sulphite anhydrous
JP: Dried sodium sulfite
PhEur: Natrii sulfis anhydricus
USPNF: Sodium sulfite anhydrous

2 Synonyms

Anhydrous sodium sulfite; disodium sulfite; exsiccated sodium sulfite; E221; sulfurous acid disodium salt.

3 Chemical Name and CAS Registry Number

Sodium sulfite [7757-83-7]

4 Empirical Formula and Molecular Weight

Na_2SO_3 126.04

5 Structural Formula

Na_2SO_3

6 Functional Category

Antimicrobial preservative; antioxidant.

7 Applications in Pharmaceutical Formulation or Technology

Sodium sulfite is used as an antioxidant in applications similar to those for sodium metabisulfite(1) It is also an effective antimicrobial preservative, particularly against fungi at low pH (0.1% w/v of sodium sulfite is used). Sodium sulfite is used in cosmetics, food products, and pharmaceutical applications such as parenteral formulations, inhalations, oral formulations, and topical preparations.

See also Sodium Metabisulfite.

8 Description

Sodium sulfite occurs as an odorless white powder or hexagonal prisms. Note that the commercially available sodium sulfite is often presented as a white to tan- or pink-colored powder that would not conform to the pharmacopeial specification.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium sulfite.

Test	JP 2001	PhEur 2005	USPNF 23
Characters	+	+	—
Identification	+	+	+
Appearance of solution	—	+	+
Heavy metals	⩽20 ppm	⩽10 ppm	⩽10 ppm
Iron	—	⩽10 ppm	⩽10 ppm
Selenium	—	⩽10 ppm	⩽10 ppm
Thiosulfates	+	⩽0.1%	+
Zinc	—	⩽25 ppm	⩽25 ppm
Assay	⩾97%	95.0–100.5%	95.0–100.5%

10 Typical Properties

Acidity/alkalinity: pH = 9 for an aqueous solution.
Density: $2.633\ g/cm^3$
Hygroscopicity: hygroscopic.
Solubility: soluble 1 in 3.2 parts of water; soluble in glycerin; practically insoluble in ethanol (95%).

11 Stability and Storage Conditions

Sodium sulfite should be stored in a well-closed container in a cool, dry, place. In solution, sodium sulfite is slowly oxidized to sulfate by dissolved oxygen; strong acids lead to formation of sulfurous acid/sulfur dioxide. On heating, sodium sulfite decomposes liberating sulfur oxides.

12 Incompatibilities

Sodium sulfite is incompatible with acids, oxidizing agents, many proteins, and vitamin B_1. *See also* Sodium Metabisulfite.

13 Method of Manufacture

Sodium bisulfite is prepared by reacting sulfur dioxide gas with sodium hydroxide solution. The solid material is obtained by evaporation of water. Further neutralization with sodium hydroxide while keeping the temperature above 33.6°C leads to crystallization of the anhydrous sodium sulfite (below this temperature the heptahydrate form is obtained).

14 Safety

Sodium sulfite is widely used in food and pharmaceutical applications as an antioxidant. It is generally regarded as relatively nontoxic and nonirritant when used as an excipient.(2,3) However, contact dermatitis and hypersensitivity reactions have been reported.(4,5) The acceptable daily intake for sodium sulfite has been set at up to 350 μg/kg bodyweight daily.(6)

LD_{50} (mouse, IP): 0.950 g/kg(7)
LD_{50} (mouse, IV): 0.130 g/kg
LD_{50} (mouse, oral): 0.820 g/kg
LD_{50} (rabbit, IV): 0.065 g/kg
LD_{50} (rabbit, oral): 1.181 g/kg
LD_{50} (rat, IV): 0.115 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in FDA Inactive Ingredients Guide (epidural, IM, IV, and SC injections; inhalation solution; ophthalmic solutions; oral syrups and suspensions; otic solutions; topical creams and emulsions). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Sodium sulfite heptahydrate; sodium metabisulfite.

Sodium sulfite heptahydrate

Synonyms: natrii sulfis heptahydricus.
CAS number: [7785-83-7]
Molecular weight: 252.15
Description: colorless crystals.
Density: 1.56 g/cm^3
Solubility: 1 in 1.6 of water; 1 in 30 of glycerin; sparingly soluble in ethanol (95%).
Comments: sodium sulfite heptahydrate is included in the PhEur 2005. The heptahydrate is unstable, oxidizing in the air to the sulfate.

18 Comments

The EINECS number for sodium sulfite is 231-821-4.

19 Specific References

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20 General References

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21 Authors

HJ de Jong.

22 Date of Revision

17 August 2005.

Sorbic Acid

1 Nonproprietary Names

BP: Sorbic acid
PhEur: Acidum sorbicum
USPNF: Sorbic acid

2 Synonyms

E200; (2-butenylidene) acetic acid; crotylidene acetic acid; hexadienic acid; hexadienoic acid; 2,4-hexadienoic acid; 1,3-pentadiene-1-carboxylic acid; 2-propenylacrylic acid; (*E*,*E*)-sorbic acid; *Sorbistat K*.

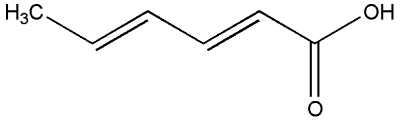
3 Chemical Name and CAS Registry Number

(*E*,*E*)-Hexa-2,4-dienoic acid [22500-92-1]

4 Empirical Formula and Molecular Weight

$C_6H_8O_2$ 112.13

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

Sorbic acid is an antimicrobial preservative(1) with antibacterial and antifungal properties used in pharmaceuticals, foods, enteral preparations, and cosmetics. Generally, it is used at concentrations of 0.05–0.2% in oral and topical pharmaceutical formulations, especially those containing nonionic surfactants. Sorbic acid is also used with proteins, enzymes, gelatin, and vegetable gums.(2) It has been shown to be an effective preservative for promethazine hydrochloride solutions in a concentration of 1 g/L.(3)

Sorbic acid has limited stability and activity against bacteria and is thus frequently used in combination with other antimicrobial preservatives or glycols, when synergistic effects appear to occur; *see* Section 10.

8 Description

Sorbic acid is a tasteless, white to yellow-white crystalline powder with a faint characteristic odor.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sorbic acid.

Test	PhEur 2005	USPNF 23
Identification	+	+
Appearance of solution	+	—
Melting range	132–136°C	132–135°C
Water	⩽1.0%	⩽0.5%
Residue on ignition	—	⩽0.2%
Sulfated ash	⩽0.2%	—
Heavy metals	⩽10 ppm	⩽0.001%
Aldehyde (as C_2H_4O)	⩽0.15%	—
Organic volatile impurities	—	+
Assay (anhydrous basis)	99.0–101.0%	99.0–101.0%

10 Typical Properties

Antimicrobial activity: sorbic acid is primarily used as an antifungal agent, although it also possesses antibacterial properties. The optimum antibacterial activity is obtained at pH 4.5; and practically no activity is observed above pH 6.(4,5) The efficacy of sorbic acid is enhanced when it is used in combination with other antimicrobial preservatives or glycols since synergistic effects occur.(6) Reported minimum inhibitory concentrations (MICs) at pH 6 are shown in Table II.(7)

Table II: Minimum inhibitory concentrations (MICs) of sorbic acid at pH 6.

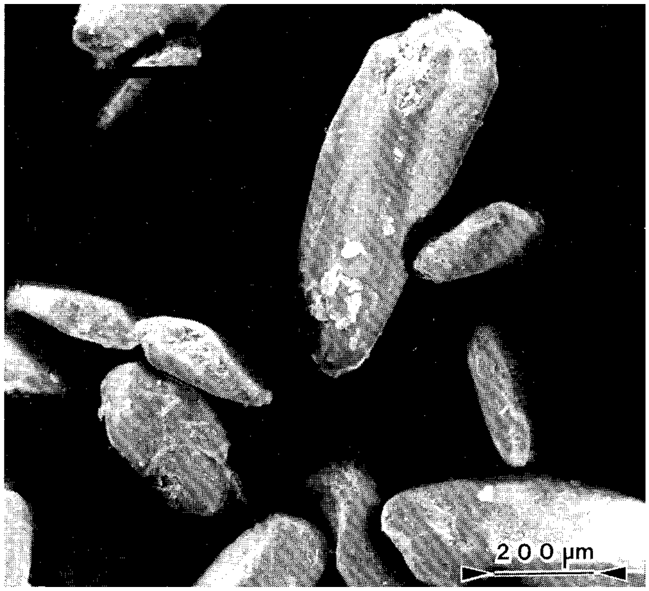
Microorganism	MIC (μg/mL)
Aspergillus niger	200–500
Candida albicans	25–50
Clostridium sporogenes	100–500
Escherichia coli	50–100
Klebsiella pneumoniae	50–100
Penicillium notatum	200–300
Pseudomonas aeruginosa	100–300
Pseudomonas cepacia	50–100
Pseudomonas fluorescens	100–300
Saccharomyces cerevisiae	200–500
Staphylococcus aureus	50–100

Boiling point: 228°C with decomposition.
Density: 1.20 g/cm^3
Dissociation constant: $pK_a = 4.76$
Flash point: 127°C
Melting point: 134.5°C
Solubility: *see* Table III. In syrup, the solubility of sorbic acid decreases with increasing sugar content.
Vapor pressure: <1.3 Pa (<0.01 mmHg) at 20°C

Table III: Solubility of sorbic acid.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	1 in 11
Chloroform	1 in 15
Ethanol	1 in 8
Ethanol (95%)	1 in 10
Ether	1 in 30
Glycerin	1 in 320
Methanol	1 in 8
Propylene glycol	1 in 19
Water	1 in 400 at 30°C 1 in 26 at 100°C

SEM: 1
Excipient: Sorbic acid
Manufacturer: Pfizer Ltd.
Magnification: 60×



11 Stability and Storage Conditions

Sorbic acid is sensitive to oxidation, particularly in the presence of light; oxidation occurs more readily in aqueous solution than in the solid form. Sorbic acid may be stabilized by phenolic antioxidants such as 0.02% propyl gallate.(6)

Sorbic acid is combustible when exposed to heat or flame. When heated to decomposition, it emits acrid smoke and irritating fumes. The bulk material should be stored in a well-closed container, protected from light, at a temperature not exceeding 40°C.

12 Incompatibilities

Sorbic acid is incompatible with bases, oxidizing agents, and reducing agents. Some loss of antimicrobial activity occurs in the presence of nonionic surfactants and plastics. Oxidation is catalyzed by heavy-metal salts. Sorbic acid will also react with sulfur-containing amino acids, although this can be prevented by the addition of ascorbic acid, propyl gallate, or butylhydroxytoluene.

When stored in glass containers, the solution becomes very pH sensitive; therefore, preparations using sorbic acid as a preservative should be tested for their microbial purity after prolonged periods of storage.

Aqueous solutions of sorbic acid without the addition of antioxidants are rapidly decomposed when stored in polypropylene, polyvinylchloride, and polyethylene containers.

13 Method of Manufacture

Naturally occurring sorbic acid may be extracted as the lactone (parasorbic acid) from the berries of the mountain ash *Sorbus aucuparia* L. (Fam. Rosaceae). Synthetically, sorbic acid may be prepared by the condensation of crotonaldehyde and ketene in the presence of boron trifluoride; by the condensation of crotonaldehyde and malonic acid in pyridine solution; or from 1,1,3,5-tetraalkoxyhexane. Fermentation of sorbaldehyde or sorbitol with bacteria in a culture medium has also been used.

14 Safety

Sorbic acid is used as an antimicrobial preservative in oral and topical pharmaceutical formulations and is generally regarded as a nontoxic material. However, adverse reactions to sorbic acid and potassium sorbate, including irritant skin reactions(8–11) and allergic hypersensitivity skin reactions (which are less frequent), have been reported.(12–14)

Other adverse reactions that have been reported include exfoliative dermatitis due to ointments that contain sorbic acid,(15) and allergic conjunctivitis caused by contact lens solutions preserved with sorbic acid.(16)

No adverse reactions have been described after systemic administration of sorbic acid, and it has been reported that it can be ingested safely by patients who are allergic to sorbic acid.(17) However, perioral contact urticaria has been reported.(11)

The WHO has set an estimated total acceptable daily intake for sorbic acid, calcium sorbate, potassium sorbate, and sodium sorbate, expressed as sorbic acid, at up to 25 mg/kg bodyweight.(18,19)

Animal toxicological studies have shown no mammalian carcinogenicity or teratogenicity for sorbic acid consumed at up to 10% of the diet.(20)

LD$_{50}$ (mouse, IP): 2.82 g/kg(21)
LD$_{50}$ (mouse, oral): 3.20 g/kg
LD$_{50}$ (mouse, SC): 2.82 g/kg
LD$_{50}$ (rat, oral): 7.36 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sorbic acid can be irritant to the skin, eyes, and respiratory system. Eye protection, gloves, and a dust mask or respirator are recommended.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (ophthalmic solutions; oral capsules, solutions, syrups, tablets, topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Calcium sorbate; potassium sorbate; sodium sorbate.

Calcium sorbate

Empirical formula: $C_{12}H_{14}O_4Ca$
Synonyms: E203
Molecular weight: 262.33
CAS number: [7492-55-9]
Appearance: white, odorless, tasteless, crystalline powder.
Solubility: soluble 1 in 83 parts of water; practically insoluble in fats.
Comments: the EINECS number for calcium sorbate is 231-321-6.

Sodium sorbate

Empirical formula: $C_6H_7O_2Na$
Synonyms: E201; sodium (*E*,*E*)-hexa-2,4-dienoate.
Molecular weight: 134.12
CAS number: [42788-83-0]
Appearance: light, white, crystalline powder.
Solubility: soluble 1 in 3 parts of water.
Comments: the EINECS number for sodium sorbate is 231-819-3.

18 Comments

The *trans*,*trans*-isomer of sorbic acid is the commercial product. A specification for sorbic acid is contained in the Food Chemicals Codex (FCC).

The EINECS number for sorbic acid is 203-768-7.

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21 Authors

W Cook.

22 Date of Revision

4 August 2005.

Sorbitan Esters (Sorbitan Fatty Acid Esters)

1 Nonproprietary Names

BP: Sorbitan laurate
Sorbitan oleate
Sorbitan palmitate
Sorbitan stearate
Sorbitan trioleate
JP: Sorbitan sesquioleate
PhEur: Sorbitani lauras
Sorbitani oleas
Sorbitani palmitas
Sorbitani sesquioleas
Sorbitani stearas
Sorbitani trioleas
USPNF: Sorbitan monolaurate (sorbitan, esters monodecanoate)
Sorbitan monooleate
Sorbitan monopalmitate
Sorbitan monostearate
Sorbitan sesquioleate
Sorbitan trioleate

2 Synonyms

See Table I.

3 Chemical Names and CAS Registry Numbers

See Table II.

Table II: Chemical name and CAS Registry Number of selected sorbitan esters.

Name	Chemical name	CAS number
Sorbitan diisostearate	Sorbitan diisooctadecanoate	[68238-87-9]
Sorbitan dioleate	(*Z,Z*)-Sorbitan di-9-octadecanoate	[29116-98-1]
Sorbitan monolaurate	Sorbitan monododecanoate	[1338-39-2]
Sorbitan monoisostearate	Sorbitan monoisooctadecanoate	[71902-01-7]
Sorbitan monooleate	(*Z*)-Sorbitan mono-9-octadecenoate	[1338-43-8]
Sorbitan monopalmitate	Sorbitan monohexadecanoate	[26266-57-9]
Sorbitan monostearate	Sorbitan mono-octadecanoate	[1338-41-6]
Sorbitan sesquiisostearate	Sorbitan sesquiisooctadecanoate	[71812-38-9]
Sorbitan sesquioleate	(*Z*)-Sorbitan sesqui-9-octadecenoate	[8007-43-0]
Sorbitan sesquistearate	Sorbitan sesqui-octadecanoate	[51938-44-4]
Sorbitan triisostearate	Sorbitan triisooctadecanoate	[54392-27-7]
Sorbitan trioleate	(*Z,Z,Z*)-Sorbitan tri-9-octadecenoate	[26266-58-0]
Sorbitan tristearate	Sorbitan tri-octadecanoate	[26658-19-5]

4 Empirical Formula and Molecular Weight

See Table III.

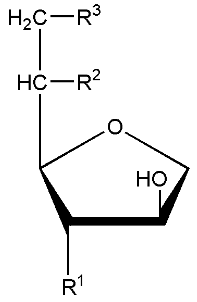
Table I: Synonyms of selected sorbitan esters.

Name	Synonym
Sorbitan monoisostearate	1,4-Anhydro-D-glucitol, 6-isooctadecanoate; anhydrosorbitol monoisostearate; *Arlacel 987*; *Crill 6*; sorbitan isostearate.
Sorbitan monolaurate	*Arlacel 20*; *Armotan ML*; *Crill 1*; *Dehymuls SML*; E493; *Glycomul L*; *Hodag SML*; *Liposorb L*; *Montane 20*; *Protachem SML*; *Sorbester P12*; *Sorbirol L*; sorbitan laurate; *Span 20*; *Tego SML*.
Sorbitan monooleate	*Ablunol S-80*; *Arlacel 80*; *Armotan MO*; *Capmul O*; *Crill 4*; *Crill 50*; *Dehymuls SMO*; *Drewmulse SMO*; *Drewsorb 80K*; E494; *Glycomul O*; *Hodag SMO*; *Lamesorb SMO*; *Liposorb O*; *Montane 80*; *Nikkol SO-10*; *Nissan Nonion OP-80R*; *Norfox Sorbo S-80*; *Polycon S80 K*; *Proto-sorb SMO*; *Protachem SMO*; *S-Maz 80K*; *Sorbester P17*; *Sorbirol O*; sorbitan oleate; *Sorgen 40*; *Sorgon S-40-H*; *Span 80*; *Tego SMO*.
Sorbitan monopalmitate	1,4-Anhydro-D-glucitol, 6-hexadecanoate; *Ablunol S-40*; *Arlacel 40*; *Armotan MP*; *Crill 2*; *Dehymuls SMP*; E495; *Glycomul P*; *Hodag SMP*; *Lamesorb SMP*; *Liposorb P*; *Montane 40*; *Nikkol SP-10*; *Nissan Nonion PP-40R*; *Protachem SMP*; *Proto-sorb SMP*; *Sorbester P16*; *Sorbirol P*; sorbitan palmitate; *Span 40*.
Sorbitan monostearate	*Ablunol S-60*; *Alkamuls SMS*; 1,4-Anhydro-D-glucitol, 6-octadecanoate; anhydrosorbitol monostearate; *Arlacel 60*; *Armotan MS*; *Atlas 110K*; *Capmul S*; *Crill 3*; *Dehymuls SMS*; *Drewmulse SMS*; *Drewsorb 60K*; *Durtan 6O*; *Durtan 60K*; E491; *Famodan MS Kosher*; *Glycomul S FG*; *Glycomul S KFG*; *Hodag SMS*; *Lamesorb SMS*; *Liposorb S*; *Liposorb SC*; *Liposorb S-K*; *Montane 60*; *Nissan Nonion SP-60R*; *Norfox Sorbo S-60FG*; *Polycon S60K*; *Protachem SMS*; *Prote-sorb SMS*; *S-Maz 60K*; *S-Maz 60KHS*; *Sorbester P18*; *Sorbirol S*; sorbitan stearate; *Sorgen 50*; *Span 60*; *Span 60K*; *Span 60 VS*; *Tego SMS*.
Sorbitan sesquiisostearate	*Protachem SQI*.
Sorbitan sesquioleate	*Arlacel C*; *Arlacel 83*; *Crill 43*; *Glycomul SOC*; *Hodag SSO*; *Liposorb SQO*; *Montane 83*; *Nikkol SO-15*; *Nissan Nonion OP-83RAT*; *Protachem SOC*; *Sorgen 30*; *Sorgen S-30-H*.
Sorbitan trilaurate	*Span 25*.
Sorbitan trioleate	*Ablunol S-85*; *Arlacel 85*; *Crill 45*; *Glycomul TO*; *Hodag STO*; *Liposorb TO*; *Montane 85*; *Nissan Nonion OP-85R*; *Protachem STO*; *Prote- sorb STO*; *S-Maz 85K*; *Sorbester P37*; *Span 85*; *Tego STO*.
Sorbitan tristearate	*Alkamuls STS*; *Crill 35*; *Crill 41*; *Drewsorb 65K*; E492; *Famodan TS Kosher*; *Glycomul TS KFG*; *Hodag STS*; *Lamesorb STS*; *Liposorb TS*; *Liposorb TS-K*; *Montane 65*; *Protachem STS*; *Proteo-sorb STS*; *Sorbester P38*; *Span 65*; *Span 65K*.

Table III: Empirical formula and molecular weight of selected sorbitan esters.

Name	Formula	Molecular weight
Sorbitan diisostearate	$C_{42}H_{80}O_7$	697
Sorbitan dioleate	$C_{42}H_{76}O_7$	693
Sorbitan monoisostearate	$C_{24}H_{46}O_6$	431
Sorbitan monolaurate	$C_{18}H_{34}O_6$	346
Sorbitan monooleate	$C_{24}H_{44}O_6$	429
Sorbitan monopalmitate	$C_{22}H_{42}O_6$	403
Sorbitan monostearate	$C_{24}H_{46}O_6$	431
Sorbitan sesquiisostearate	$C_{33}H_{63}O_{6.5}$	564
Sorbitan sesquioleate	$C_{33}H_{60}O_{6.5}$	561
Sorbitan sesquistearate	$C_{33}H_{63}O_{6.5}$	564
Sorbitan triisostearate	$C_{60}H_{114}O_8$	964
Sorbitan trioleate	$C_{60}H_{108}O_8$	958
Sorbitan tristearate	$C_{60}H_{114}O_8$	964

5 Structural Formula



$R^1 = R^2 = OH$, $R^3 = R$ (see below) for sorbitan monoesters
$R^1 = OH$, $R^2 = R^3 = R$ for sorbitan diesters
$R^1 = R^2 = R^3 = R$ for sorbitan triesters
where R =
$(C_{17}H_{35})COO$ for isostearate
$(C_{11}H_{23})COO$ for laurate
$(C_{17}H_{33})COO$ for oleate
$(C_{15}H_{31})COO$ for palmitate
$(C_{17}H_{35})COO$ for stearate

The sesquiesters are equimolar mixtures of monoesters and diesters.

6 Functional Category

Emulsifying agent; nonionic surfactant; solubilizing agent; wetting and dispersing/suspending agent.

7 Applications in Pharmaceutical Formulation or Technology

Sorbitan monoesters are a series of mixtures of partial esters of sorbitol and its mono- and dianhydrides with fatty acids. Sorbitan diesters are a series of mixtures of partial esters of sorbitol and its monoanhydride with fatty acids.

Sorbitan esters are widely used in cosmetics, food products, and pharmaceutical formulations as lipophilic nonionic surfactants. They are mainly used in pharmaceutical formulations as emulsifying agents in the preparation of creams, emulsions, and ointments for topical application. When used alone, sorbitan esters produce stable water-in-oil emulsions and microemulsions but are frequently used in combination with varying proportions of a polysorbate to produce water-in-oil or oil-in-water emulsions or creams of varying consistencies.

Sorbitan monolaurate, sorbitan monopalmitate and sorbitan trioleate have also been used at concentrations of 0.01–0.05% w/v in the preparation of an emulsion for intramuscular administration. *See* Table IV.

Table IV: Uses of sorbitan esters.

Use	Concentration (%)
Emulsifying agent	
Used alone in water-in-oil emulsions	1–15
Used in combination with hydrophilic emulsifiers in oil-in-water emulsions	1–10
Used to increase the water-holding properties of ointments	1–10
Solubilizing agent	
For poorly soluble, active constituents in lipophilic bases	1–10
Wetting agent	
For insoluble, active constituents in lipophilic bases	0.1–3

8 Description

Sorbitan esters occur as cream- to amber-colored liquids or solids with a distinctive odor and taste; *see* Table V.

Table V: Appearance of selected sorbitan esters.

Name	Appearance
Sorbitan monoisostearate	Yellow viscous liquid
Sorbitan monolaurate	Yellow viscous liquid
Sorbitan monooleate	Yellow viscous liquid
Sorbitan monopalmitate	Cream solid
Sorbitan monostearate	Cream solid
Sorbitan sesquioleate	Amber viscous liquid
Sorbitan trioleate	Amber viscous liquid
Sorbitan tristearate	Cream/yellow solid

9 Pharmacopeial Specifications

See Table VI.

10 Typical Properties

Acid value: *see* Table VII.
Density: *see* Table VII.
Flash point: >149°C
HLB value: *see* Table VII.
Hydroxyl value: *see* Table VII.
Iodine number: *see* Table VII.
Melting point: *see* Table VII.
Moisture content: *see* Table VIII.
Pour point: *see* Table VII.
Saponification value: *see* Table VIII.
Solubility: sorbitan esters are generally soluble or dispersible in oils; they are also soluble in most organic solvents. In water, although insoluble, they are generally dispersible.
Surface tension: *see* Table VIII.
Viscosity (dynamic): *see* Table VIII.

Table VI: Pharmacopeial specifications for sorbitan esters.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Acid value			
Sorbitan monolaurate	—	⩽7.0	⩽8
Sorbitan monooleate	—	⩽8.0	⩽8
Sorbitan monopalmitate	—	⩽8.0	⩽8
Sorbitan monostearate	—	⩽10.0	⩽10
Sorbitan sesquioleate	—	⩽16.0	⩽14
Sorbitan trioleate	—	⩽16.0	⩽17
Hydroxyl value			
Sorbitan monolaurate	—	330–358	330–358
Sorbitan monooleate	—	190–210	190–215
Sorbitan monopalmitate	—	270–305	275–305
Sorbitan monostearate	—	235–260	235–260
Sorbitan sesquioleate	—	180–215	182–220
Sorbitan trioleate	—	55–75	50–75
Iodine value			
Sobitan monolaurate	—	⩽10.0	—
Sorbitan monooleate	—	62–76	62–76
Sorbitan sesquioleate	—	70–95	65–75
Sorbitan trioleate	—	76–90	77–85
Peroxide value			
Sorbitan monolaurate	—	⩽5.0	—
Sorbitan monooleate	—	⩽10.0	—
Sorbitan monopalmitate	—	⩽5.0	—
Sorbitan monostearate	—	⩽5.0	—
Sorbitan sesquioleate	—	⩽10.0	—
Sorbitan trioleate	—	⩽10.0	—
Saponification value			
Sorbitan monolaurate	—	158–170	158–170
Sorbitan monooleate	—	145–160	145–160
Sorbitan monopalmitate	—	140–155	140–150
Sorbitan monostearate	—	147–157	147–157
Sorbitan sesquioleate	150–168	145–166	143–165
Sorbitan trioleate	—	170–190	169–183
Water			
Sorbitan monolaurate	—	⩽1.5%	⩽1.5%
Sorbitan monooleate	—	⩽1.5%	⩽1.0%
Sorbitan monopalmitate	—	⩽1.5%	⩽1.5%
Sorbitan monostearate	—	⩽1.5%	⩽1.5%
Sorbitan sesquioleate	⩽3.0%	⩽1.5%	⩽1.0%
Sorbitan trioleate	—	⩽1.5%	⩽0.7%
Residue on ignition			
Sorbitan monolaurate	—	—	⩽0.5%
Sorbitan monooleate	—	—	⩽0.5%
Sorbitan monopalmitate	—	—	⩽0.5%
Sorbitan monostearate	—	—	⩽0.5%
Sorbitan sesquioleate	⩽1.0%	—	⩽1.4%
Sorbitan trioleate	—	—	⩽0.25%
Total ash	—	⩽0.5%	—
Heavy metals	⩽20 ppm	⩽10 ppm	⩽0.001%
Arsenic	⩽2 ppm	—	—
Specific gravity			
Sorbitan laurate	—	≈0.98	—
Sorbitan oleate	—	≈0.99	—
Sorbitan sesquioleate	0.960–1.020	≈0.99	—
Melting point			
Sorbitan palmitate	—	44–51°C	—
Sorbitan monostearate	—	50–60°C	—
Organic volatile impurities	—	—	+
Assay for fatty acids			
Sorbitan monolaurate	—	+	55.0–63.0%

Continued

Table VI: Continued

Test	JP 2001	PhEur 2005	USPNF 23
Sorbitan monooleate	—	+	72.0–78.0%
Sorbitan monopalmitate	—	+	63.0–71.0%
Sorbitan monostearate	—	+	68.0–76.0%
Sorbitan sesquioleate	—	+	74.0–80.0%
Sorbitan trioleate	—	+	85.5–90.0%
Assay for polyols			
Sorbitan monolaurate	—	—	39.0–45.0%
Sorbitan monooleate	—	—	25.0–31.0%
Sorbitan monopalmitate	—	—	32.0–38.0%
Sorbitan monostearate	—	—	27.0–34.0%
Sorbitan sesquioleate	—	—	22.0–28.0%
Sorbitan trioleate	—	—	13.0–19.0%

Table VII: Typical properties of selected sorbitan esters.

Name	Acid value	Density (g/cm^3)	HLB value	Hydroxyl value	Iodine number	Melting point (°C)	Pour point (°C)
Sorbitan monoisostearate	⩽8	—	4.7	220–250	—	—	—
Sorbitan monolaurate	⩽7	1.01	8.6	159–169	⩽7	—	16–20
Sorbitan monooleate	⩽8	1.01	4.3	193–209	—	—	−12
Sorbitan monopalmitate	3–7	1.0	6.7	270–303	⩽1	43–48	—
Sorbitan monostearate	5–10	—	4.7	235–260	⩽1	53–57	—
Sorbitan sesquioleate	8.5–13	1.0	3.7	188–210	—	—	—
Sorbitan trioleate	10–14	0.95	1.8	55–70	—	—	—
Sorbitan tristearate	⩽7	—	2.1	60–80	—	—	—

Table VIII: Typical properties of selected sorbitan esters.

Name	Saponification value	Surface tension of 1% aqueous solution (mN/m)	Viscosity at 25°C (mPa s)	Water content (%)
Sorbitan monoisostearate	143–153	—	—	⩽1.0
Sorbitan monolaurate	159–169	28	3900–4900	⩽0.5
Sorbitan monooleate	149–160	30	970–1080	⩽0.5
Sorbitan monopalmitate	142–152	36	Solid	⩽1.0
Sorbitan monostearate	147–157	46	Solid	⩽1.0
Sorbitan sesquioleate	149–160	—	1500	⩽1.0
Sorbitan trioleate	170–190	32	200–250	⩽1.0
Sorbitan tristearate	172–185	48	Solid	⩽1.0

11 Stability and Storage Conditions

Gradual soap formation occurs with strong acids or bases; sorbitan esters are stable in weak acids or bases.

Sorbitan esters should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

—

13 Method of Manufacture

Sorbitol is dehydrated to form a hexitan (1,4-sorbitan), which is then esterified with the desired fatty acid.

14 Safety

Sorbitan esters are widely used in cosmetics, food products, and oral and topical pharmaceutical formulations and are generally regarded as nontoxic and nonirritant materials. However, there have been occasional reports of hypersensitive skin reactions following the topical application of products containing sorbitan esters.(1–4) When heated to decomposition, the sorbitan esters emit acrid smoke and irritating fumes.

The WHO has set an estimated acceptable daily intake of sorbitan monopalmitate, monostearate, and tristearate,(5) and of sorbitan monolaurate and monooleate(6) at up to 25 mg/kg body-weight calculated as total sorbitan esters.

Sorbitan monolaurate: LD_{50} (rat, oral): 33.6 g/kg.(7)
Experimental neoplastigen.
Sorbitan monostearate: LD_{50} (rat, oral): 31 g/kg.(7)
Very mildly toxic by ingestion. Experimental reproductive effects.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16 Regulatory Status

Certain sorbitan esters are accepted as food additives in the UK. Sorbitan esters are included in the FDA Inactive Ingredients Guide (inhalations; IM injections; ophthalmic, oral, topical, and vaginal preparations). Sorbitan esters are used in nonparenteral medicines licensed in the UK. Sorbitan esters are included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Polyoxyethylene sorbitan fatty acid esters.

18 Comments

EINECS numbers

Sorbitan diisostearate	[269-410-7]
Sorbitan dioleate	[249-448-0]
Sorbitan laurate	[215-663-3]
Sorbitan oleate	[215-665-4]
Sorbitan palmitate	[247-568-8]
Sorbitan sesquiolate	[232-360-1]
Sorbitan sesquistearate	[257-529-7]
Sorbitan stearate	[215-664-9]
Sorbitan triisostearate	[259-141-3]
Sorbitan trioleate	[247-569-3]
Sorbitan tristearate	247-891-4

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21 Authors

MJ Lawrence.

22 Date of Revision

22 August 2005.

Sorbitol

1 Nonproprietary Names

BP: Sorbitol
JP: D-Sorbitol
PhEur: Sorbitolum
USPNF: Sorbitol

2 Synonyms

*C*PharmSorbidex*; E420; 1,2,3,4,5,6-hexanehexol; *Liponic 70-NC*; *Liponic 76-NC*; *Meritol*; *Neosorb*; sorbite; D-sorbitol; *Sorbitol Instant*; *Sorbogem.*

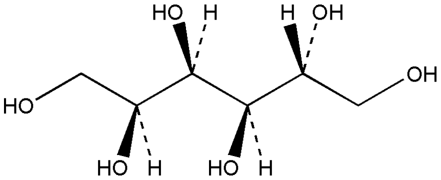
3 Chemical Name and CAS Registry Number

D-Glucitol [50-70-4]

4 Empirical Formula and Molecular Weight

$C_6H_{14}O_6$ 182.17

5 Structural Formula



6 Functional Category

Humectant; plasticizer; sweetening agent; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Sorbitol is widely used as an excipient in pharmaceutical formulations. It is also used extensively in cosmetics and food products; *see* Table I.

Sorbitol is used as a diluent in tablet formulations prepared by either wet granulation or direct compression.(1–5) It is particularly useful in chewable tablets owing to its pleasant, sweet taste and cooling sensation. In capsule formulations it is used as a plasticizer for gelatin. Sorbitol has been used as a plasticizer in film formulations.(6,7)

In liquid preparations(8) sorbitol is used as a vehicle in sugar-free formulations and as a stabilizer for drug,(9) vitamin,(10,11) and antacid suspensions. It has also been shown to be a suitable carrier to enhance the *in vitro* dissolution rate of indometacin.(12) In syrups it is effective in preventing crystallization around the cap of bottles. Sorbitol is additionally used in injectable(13) and topical preparations and therapeutically as an osmotic laxative.

Sorbitol may also be used analytically as a marker for assessing liver blood flow.(14)

Table I: Uses of sorbitol.

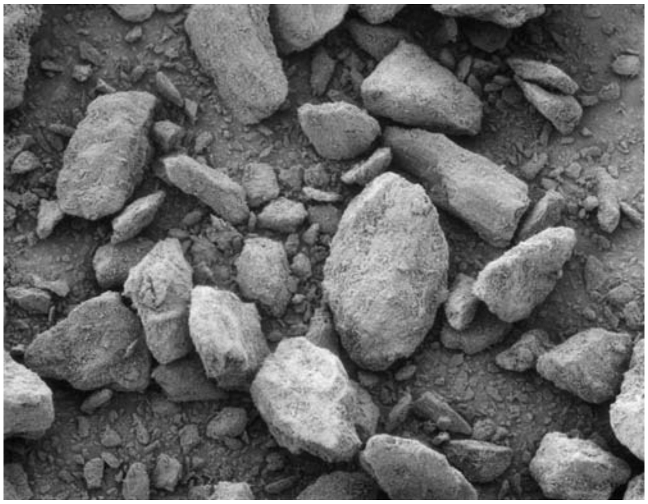
Use	Concentration (%)
Humectant	3–15
IM injections	10–25
Moisture control agent in tablets	3–10
Oral solutions	20–35
Oral suspensions	70
Plasticizer for gelatin and cellulose	5–20
Prevention of 'cap locking' in syrups and elixirs	15–30
Substitute for glycerin and propylene glycol	25–90
Tablet binder and filler	25–90
Toothpastes	20–60
Topical emulsions	2–18

8 Description

Sorbitol is D-glucitol. It is a hexahydric alcohol related to mannose and is isomeric with mannitol.

Sorbitol occurs as an odorless, white or almost colorless, crystalline, hygroscopic powder. Four crystalline polymorphs and one amorphous form of sorbitol have been identified that have slightly different physical properties, e.g., melting point.(3) Sorbitol is available in a wide range of grades and polymorphic forms such as granules, flakes, or pellets that tend to cake less than the powdered form and have more desirable compression characteristics. Sorbitol has a pleasant, cooling, sweet taste and has approximately 50–60% of the sweetness of sucrose.

SEM: 1
Excipient: Sorbitol
Manufacturer: SPI Pharma
Lot No.: 5224F8
Magnification: 100×



9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Acidity/alkalinity: pH = 4.5–7.0 for a 10% w/v aqueous solution.

Compressibility: compression characteristics and the degree of lubrication required vary, depending upon the particle size and grade of sorbitol used.

Density: 1.49 g/cm^3

Density (bulk): 0.448 g/cm^3

Density (tapped): 0.400 g/cm^3

Density (true): 1.507 g/cm^3

Flowability: flow characteristics vary depending upon the particle size and grade of sorbitol used. Fine powder grades tend to be poorly flowing, while granular grades have good flow properties.

Heat of solution: −110.9 J/g (–26.5 cal/g)

Melting point:

Anhydrous form: 110–112°C;
Gamma polymorph: 97.7°C;
Metastable form: 93°C.

Moisture content: sorbitol is a very hygroscopic powder and relative humidities greater than 60% at 25°C should be avoided when sorbitol is added to direct-compression tablet formulas. *See also* Figure 1.

Table II: Pharmacopeial specifications for sorbitol.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	+	+	—
Acidity or alkalinity	+	—	—
pH	—	—	3.5–7.0
Appearance of solution	+	+	+
Arsenic	⩽1.3 ppm	—	—
Chloride	⩽0.005%	—	⩽0.005%
Sulfate	⩽0.006%	—	⩽0.01%
Conductivity	—	⩽20 μS·cm^{-1}	—
Glucose	+	—	—
Heavy metals	⩽5 ppm	—	—
Lead	—	⩽0.5 ppm	—
Microbial contamination	—	+	—
Bacterial	—	⩽10^2/g	⩽10^3/g
Fungi	—	⩽10^2/g	⩽10^2/g
Bacterial endotoxins	—	+	+
Nickel	+	⩽1 ppm	⩽1 μg/g
Organic volatile impurities	—	—	+
Reducing sugars	—	⩽0.2%	⩽0.3%
Related products	—	⩽0.1%	—
Residue on ignition	⩽0.02%	—	⩽0.1%
Total sugars	+	—	—
Water	⩽2.0%	⩽1.5%	⩽1.5%
Assay (anhydrous basis)	⩾97.0%	97.0–102.0%	91.0–100.5%

Osmolarity: a 5.48% w/v aqueous solution of sorbitol hemihydrate is isoosmotic with serum.

Particle size distribution: particle size distribution varies depending upon the grade of sorbitol. For fine powder grades, typically 87% <125 μm in size; for granular grades, 22% <125 μm, 45% between 125 and 250 μm, and 33% between 250 and 590 μm. Individual suppliers' literature should be consulted for further information.

Solubility: *see* Table III.

See also Section 17.

Table III: Solubility of sorbitol.

Solvent	Solubility at 20°C
Chloroform	Practically insoluble
Ethanol (95%)	1 in 25
Ethanol (82%)	1 in 8.3
Ethanol (62%)	1 in 2.1
Ethanol (41%)	1 in 1.4
Ethanol (20%)	1 in 1.2
Ethanol (11%)	1 in 1.14
Ether	Practically insoluble
Methanol	Slightly soluble
Water	1 in 0.5

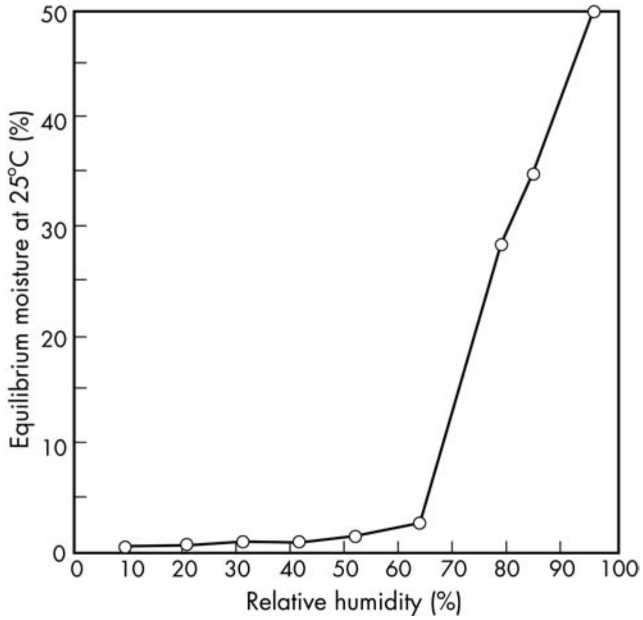


Figure 1: Equilibrium moisture content of sorbitol USPNF.

11 Stability and Storage Conditions

Sorbitol is chemically relatively inert and is compatible with most excipients. It is stable in air in the absence of catalysts and in cold, dilute acids and alkalis. Sorbitol does not darken or decompose at elevated temperatures or in the presence of amines. It is nonflammable, noncorrosive, and nonvolatile.

Although sorbitol is resistant to fermentation by many microorganisms, a preservative should be added to sorbitol solutions. Solutions may be stored in glass, plastic, aluminum, and stainless steel containers. Solutions for injection may be sterilized by autoclaving.

The bulk material is hygroscopic and should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Sorbitol will form water-soluble chelates with many divalent and trivalent metal ions in strongly acidic and alkaline conditions. Addition of liquid polyethylene glycols to sorbitol solution, with vigorous agitation, produces a waxy, water-soluble gel with a melting point of 35–40°C. Sorbitol solutions also react with iron oxide to become discolored.

Sorbitol increases the degradation rate of penicillins in neutral and aqueous solutions.(15)

13 Method of Manufacture

Sorbitol occurs naturally in the ripe berries of many trees and plants. It was first isolated in 1872 from the berries of the Mountain Ash (*Sorbus americana*).

Industrially, sorbitol is prepared by high-pressure hydrogenation with a copper–chromium or nickel catalyst, or by electrolytic reduction of glucose and corn syrup. If cane or beet sugars are used as a source, the disaccharide is hydrolyzed to dextrose and fructose prior to hydrogenation.

14 Safety

Sorbitol is widely used in a number of pharmaceutical products and occurs naturally in many edible fruits and berries. It is absorbed more slowly from the gastrointestinal tract than sucrose and is metabolized in the liver to fructose and glucose. Its caloric value is approximately 16.7 J/g (4 cal/g). Sorbitol is better tolerated by diabetics than sucrose and is widely used in many sugar-free liquid vehicles. However, it is not considered to be unconditionally safe for diabetics.

Reports of adverse reactions to sorbitol are largely due to its action as an osmotic laxative when ingested orally,(16–18) which may be exploited therapeutically. Ingestion of large quantities of sorbitol (>20 g/day in adults) should therefore be avoided.

Sorbitol is not readily fermented by oral microorganisms and has little effect on dental plaque pH; hence, it is generally considered to be noncariogenic.(19)

Sorbitol is generally considered to be more irritating than mannitol.

LD_{50} (mouse, IV): 9.48 g/kg(20)
LD_{50} (mouse, oral): 17.8 g/kg
LD_{50} (rat, IV): 7.1 g/kg
LD_{50} (rat, SC): 29.6 g/kg

15 Handling Precautions

Sorbitol may be harmful if ingested in great quantities. It may be irritant to the eyes. Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask or respirator are recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (intra-articular and IM injections; nasal; oral capsules, solutions, suspensions, syrups and tablets; rectal, topical, and vaginal preparations). Included in parenteral and nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Maltitol solution; mannitol; sorbitol solution 70%; xylitol.

Sorbitol solution 70%

Synonyms: sorbitol liquid; *Sorbo*.
Appearance: a clear, colorless and odorless, viscous liquid.
Comments: sorbitol solution is an aqueous solution of hydrogenated, partly hydrolyzed starch. For physical properties, *see* Table IV.

Table IV: Physical properties of sorbitol in water solutions.

Concentration (% w/w) at 25°C	Density (g/cm³) at 25°C	Viscosity (mPa s) at 25°C	Refractive index	Freezing point (°C)
10	1.034	1.2	1.348	−1.1
20	1.073	1.7	1.365	−3.8
30	1.114	2.5	1.383	−8.0
40	1.155	4.4	1.400	−13.0
50	1.197	9.1	1.418	−26.0
60	1.240	26.0	1.437	—
70	1.293	110.0	1.458	—
80	1.330	900.0	1.478	—

18 Comments

Sorbitol may be substituted for sucrose to prepare 70–90% w/v syrups.

Several different grades of sorbitol, with different polymorphic form, particle size, and other physical characteristics are commercially available, e.g., *Neosorb* (Roquette Frères). Pyrogen-free grades are also available from some suppliers.

A specification for sorbitol is contained in the Food Chemicals Codex (FCC). The EINECS number for sorbitol is 200-061-5.

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21 Authors

SC Owen.

22 Date of Revision

17 August 2005.

Soybean Oil

1 Nonproprietary Names

BP: Refined soya oil
JP: Soybean oil
PhEur: Soiae oleum raffinatum
USP: Soybean oil

2 Synonyms

Calchem IVO-114; *Lipex 107*; *Lipex 200*; *Shogun CT*; soja bean oil; soyabean oil; soya bean oil.

3 Chemical Name and CAS Registry Number

Soybean oil [8001-22-7]

4 Empirical Formula and Molecular Weight

A typical analysis of refined soybean oil indicates the composition of the acids, present as glycerides, to be: linoleic acid 50–57%; linolenic acid 5–10%; oleic acid 17–26%; palmitic acid 9–13%; and stearic acid 3–6%. Other acids are present in trace quantities.(1)

5 Structural Formula

See Sections 4 and 8.

6 Functional Category

Oleaginous vehicle; solvent.

7 Applications in Pharmaceutical Formulation or Technology

In pharmaceutical preparations, soybean oil emulsions are primarily used as a fat source in total parenteral nutrition (TPN) regimens.(2) Although other oils, such as peanut oil, have been used for this purpose, soybean oil is now preferred because it is associated with fewer adverse reactions. Emulsions containing soybean oil have also been used as vehicles for the oral and intravenous administration of drugs;(3,4) drug substances that have been incorporated into such emulsions include amphotericin,(5–7) diazepam, retinoids,(8) vitamins,(9) poorly water-soluble steroids,(10,11) fluorocarbons,(12,13) and insulin.(14) In addition, soybean oil has been used in the formulation of many drug delivery systems such as liposomes,(15) microspheres,(16) dry emulsions,(17) self-emulsifying systems,(18) and nanoemulsions and nanocapsules.(19)

Soybean oil may also be used in cosmetics and is consumed as an edible oil. As soybean oil has emollient properties, it is used as a bath additive in the treatment of dry skin conditions.

8 Description

The USP 28 describes soybean oil as the refined fixed oil obtained from the seeds of the soya plant *Glycine max* Merr. (Fabaceae). The PhEur 2005 defines refined soya-bean oil as the fatty oil obtained from the seeds of *Glycine soja* Sieb. and Zucc. and *Glycine max* (L.) Merr. (*G. hispida* (Moench) Maxim.) by extraction and subsequent refining; it may contain a suitable antioxidant. The PhEur 2005 also includes a monograph for Hydrogenated Soybean Oil. *See* Vegetable Oil, hydrogenated, type 1.

Soybean oil is a clear, pale-yellow colored, odorless or almost odorless liquid, with a bland taste that solidifies between −10 and −16°C.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for soybean oil.

Test	JP 2001	PhEur 2005	USP 28
Identification	—	+	—
Characters	—	+	—
Specific gravity	0.916–0.922	≈0.922	0.916–0.922
Refractive index	—	≈1.475	1.465–1.475
Heavy metals	—	—	⩽0.001%
Free fatty acids	—	—	+
Fatty acid composition	—	+	+
Acid value	⩽0.2	⩽0.5	—
Iodine value	126–140	—	120–141
Saponification value	188–195	—	180–200
Unsaponifiable matter	⩽1.0%	⩽1.5%	⩽1.0%
Cottonseed oil	—	—	+
Peroxide	—	⩽10.0 or ⩽5.0[a]	+
Alkaline impurities	—	+	—
Brassicasterol	—	⩽0.3%	—
Water	—	⩽0.1%[a]	—

[a] In soybean oil intended for parenteral use.

10 Typical Properties

Autoignition temperature: 445°C
Density: 0.916–0.922 g/cm^3 at 25°C
Flash point: 282°C
Freezing point: −10 to −16°C
Hydroxyl value: 4–8
Interfacial tension: 50 mN/m (50 dynes/cm) at 20°C.
Refractive index: $n_D^{25} = 1.471\text{–}1.475$
Solubility: practically insoluble in ethanol (95%) and water; miscible with carbon disulfide, chloroform, ether, and light petroleum.
Surface tension: 25 mN/m (25 dynes/cm) at 20°C.
Viscosity (dynamic):
172.9 mPa s (172.9 cP) at 0°C;
99.7 mPa s (99.7 cP) at 10°C;
50.09 mPa s (50.09 cP) at 25°C;
28.86 mPa s (28.86 cP) at 40°C.

11 Stability and Storage Conditions

Soybean oil is a stable material if protected from atmospheric oxygen.

The formation of undesirable flavors in soybean oil is accelerated by the presence of 0.01 ppm copper and 0.1 ppm iron, which act as catalysts for oxidation; this can be minimized by the addition of chelating agents.

Prolonged storage of soybean oil emulsions, particularly at elevated temperatures, can result in the formation of free fatty acids, with a consequent reduction in the pH of the emulsion; degradation is minimized at pH 6–7. However, soybean oil emulsions are stable at room temperature if stored under nitrogen in a light-resistant glass container. Plastic containers are permeable to oxygen and should not be used for long-term storage since oxidative degradation can occur.

The stability of soybean oil emulsions is considerably influenced by other additives in a formulation.(20–26)

Soybean oil should be stored in a well-filled, airtight, light-resistant container at a temperature not exceeding 25°C.

12 Incompatibilities

Soybean oil emulsions have been reported to be incompatible at 25°C with a number of materials including calcium chloride, calcium gluconate, magnesium chloride, phenytoin sodium, and tetracycline hydrochloride.(27) Lower concentrations of these materials, or lower storage temperatures, may result in improved compatibility. The source of the material may also affect compatibility; for example, while one injection from a particular manufacturer might be incompatible with a fat emulsion, an injection with the same amount of active drug substance from another manufacturer might be compatible.

Amphotericin B has been reported to be incompatible with soybean oil containing fat emulsions under certain conditions.(28)

Soybean oil emulsions are also incompatible with many other drug substances, IV infusion solutions, and ions (above certain concentrations).

When plastic syringes are used to store soybean oil emulsion, silicone oil may be extracted into the emulsion; swelling of the syringe pump also occurs, resulting in the necessity for increased forces to maintain the motion of the plunger.(29)

13 Method of Manufacture

Obtained by solvent extraction using petroleum hydrocarbons, or to a lesser extent by expression using continuous screw-press operations, of the seeds of either *Glycine max* (Leguminosae) or *Glycine soja* (Leguminosae). The oil is refined, deodorized, and clarified by filtration at about 0°C. Any phospholipids or sterols present are removed by refining with alkali.

14 Safety

Soybean oil is widely used intramuscularly as a drug vehicle or as a component of emulsions used in parenteral nutrition regimens; it is also consumed as an edible oil. Generally, soybean oil is regarded as an essentially nontoxic and nonirritant material. However, serious adverse reactions to soybean oil emulsions administered parenterally have been reported. These include cases of hypersensitivity,(30) CNS reactions,(31) and fat embolism.(32) Interference with the anticoagulant effect of warfarin has also been reported.(33)

Anaphylactic reactions have also been reported following the consumption of foods derived from, or containing, soy beans. Recently there has been concern at the concentration of phytoestrogens in some soy-derived products. Administration of soy protein to humans has resulted in significantly decreased serum lipid concentrations.(34)

In 1999, the UK Medical Devices Agency announced the voluntary withdrawal of a breast implant that contained soybean oil. The decision was taken because not enough was known at that time about the long-term safety and the rate of breakdown of the soybean oil in the filling and its possible effects on the body.(35)

LD_{50} (mouse, IV): 22.1 g/kg(36)
LD_{50} (rat, IV): 16.5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Spillages of soybean oil are slippery and should be covered with an inert absorbent material prior to disposal.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IV injections, oral capsules, and topical preparations). Included in nonparenteral (chewable tablets; oral capsules; topical bath additives) and parenteral (emulsions for IV injection or infusion) medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Canola oil; corn oil; cottonseed oil; peanut oil; sesame oil; sunflower oil.

18 Comments

The stability of soybean oil emulsions may be readily disturbed by the addition of other materials, and formulations containing soybean oil should therefore be evaluated carefully for their compatibility and stability.

A specification for soybean oil is contained in the Food Chemicals Codex (FCC).

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21 Authors

CG Cable.

22 Date of Revision

23 August 2005.

Starch

1 Nonproprietary Names

BP:	Maize starch Potato starch Rice starch Tapioca starch Wheat starch
JP:	Corn starch Potato starch Rice starch Wheat starch
PhEur:	Maydis amylum (maize starch) Solani amylum (potato starch) Oryzae amylum (rice starch) Tritici amylum (wheat starch)
USPNF:	Corn starch Potato starch Tapioca Wheat starch

Note that the USPNF 23 has individual monographs for corn (*Zea mays*), potato (*Solanum tuberosum*), tapioca (*Manihot utilissima* Pohl) and wheat starch (*Triticum aestivum*). The PhEur 2005 has monographs for each of these starches, except tapioca starch, along with an additional monograph for rice starch, *Oryza sativa*. Also note that the PhEur 2005 Suppl 5.0 contains an updated monograph for maize (corn) starch. The BP 2004 similarly describes maize, potato, rice, tapioca (cassava), and wheat starch in individual monographs, tapioca starch being obtained from the rhizomes of *Manihot utilissima* Pohl. The JP 2001 similarly describes corn (maize), rice, potato and wheat starch in separate monographs. *See also* Section 18.

2 Synonyms

Amido; amidon; amilo; amylum; *Aytex P*; *C*PharmGel*; *Fluftex W*; *Instant Pure-Cote*; *Melojel*; *Meritena*; *Paygel 55*; *Perfectamyl D6PH*; *Pure-Bind*; *Pure-Cote*; *Pure-Dent*; *Pure-Gel*; *Pure-Set*; *Purity 21*; *Purity 826*; *Tablet White*.

See also Sections 1 and 18.

3 Chemical Name and CAS Registry Number

Starch [9005-25-8]

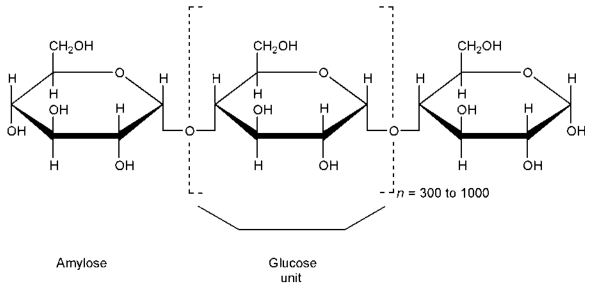
4 Empirical Formula and Molecular Weight

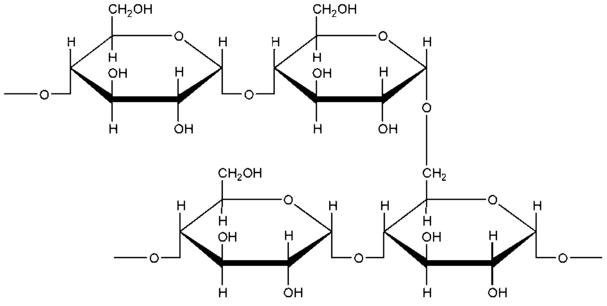
$(C_6H_{10}O_5)_n$ 50 000–160 000

where n = 300–1000.

Starch consists of amylose and amylopectin, two polysaccharides based on α-glucose. *See also* Sections 5 and 17.

5 Structural Formula





Segment of amylopectin molecule

6 Functional Category

Glidant; tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Starch is used as an excipient primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant.

As a diluent, starch is used for the preparation of standardized triturates of colorants or potent drugs to facilitate subsequent mixing or blending processes in manufacturing operations. Starch is also used in dry-filled capsule formulations for volume adjustment of the fill matrix.(1)

In tablet formulations, freshly prepared starch paste is used at a concentration of 5–25% w/w in tablet granulations as a binder. Selection of the quantity required in a given system is determined by optimization studies, using parameters such as granule friability, tablet friability, hardness, disintegration rate, and drug dissolution rate.

Starch is one of the most commonly used tablet disintegrants at concentrations of 3–15% w/w.(2–9) However, unmodified starch does not compress well and tends to increase tablet friability and capping if used in high concentrations. In granulated formulations, about half the total starch content is included in the granulation mixture and the balance as part of the final blend with the dried granulation. Also, when used as a disintegrant, starch exhibits type II isotherms and has a high specific surface for water sorption.(10)

Starch has been investigated as an excipient in novel drug delivery systems for nasal,(11,12) oral,(13–16) periodontal,(17) and other site-specific delivery systems.(18,19)

Starch is also used in topical preparations; for example, it is widely used in dusting powders for its absorbency, and is used as a protective covering in ointment formulations applied to the skin. Starch mucilage has also been applied to the skin as an emollient, has formed the base of some enemas, and has been used in the treatment of iodine poisoning.

Therapeutically, rice starch-based solutions have been used in the prevention and treatment of dehydration due to acute diarrheal diseases.

8 Description

Starch occurs as an odorless and tasteless, fine, white-colored powder comprising very small spherical or ovoid granules whose size and shape are characteristic for each botanical variety.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acidity/alkalinity: pH = 5.5–6.5 for a 2% w/v aqueous dispersion of corn starch, at 25°C.

Compressibility: *see* Figure 1.

Density (bulk): 0.462 g/cm^3 for corn starch.

Density (tapped): 0.658 g/cm^3 for corn starch.

Density (true): 1.478 g/cm^3 for corn starch.

Flowability: 10.8–11.7 g/s for corn starch;(9) 30% for corn starch (Carr compressibility index).(20) Corn starch is cohesive and has poor flow characteristics.

Gelatinization temperature: 73°C for corn starch; 72°C for potato starch; 63°C for wheat starch.

Moisture content: all starches are hygroscopic and rapidly absorb atmospheric moisture.(21,22) Approximate equilibrium moisture content values at 50% relative humidity are 11% for corn starch; 18% for potato starch; 14% for rice starch; and 13% for wheat starch. Between 30% and 80% relative humidity, corn starch is the least hygroscopic starch and potato starch is the most hygroscopic. Commercially available grades of corn starch usually contain 10–14% water. *See also* Figures 2 and 3.

Particle size distribution:

Corn starch: 2–32 μm;
Potato starch: 10–100 μm;
Rice starch: 2–20 μm;
Tapioca starch: 5–35 μm;
Wheat starch: 2–45 μm.

Median diameter for corn starch is 17 μm and for wheat starch is 23 μm.

Solubility: practically insoluble in cold ethanol (95%) and in cold water. Starch swells instantaneously in water by about 5–10% at 37°C.(2,22) Polyvalent cations produce more swelling than monovalent ions, but pH has little effect.

Specific surface area:

0.41–0.43 m^2/g for corn starch;
0.12 m^2/g for potato starch;
0.27–0.31 m^2/g for wheat starch.

Swelling temperature:

65°C for corn starch;
64°C for potato starch;
55°C for wheat starch.

Viscosity (dynamic): 13.0 mPa s (13.0 cP) for a 2% w/v aqueous dispersion of corn starch at 25°C.

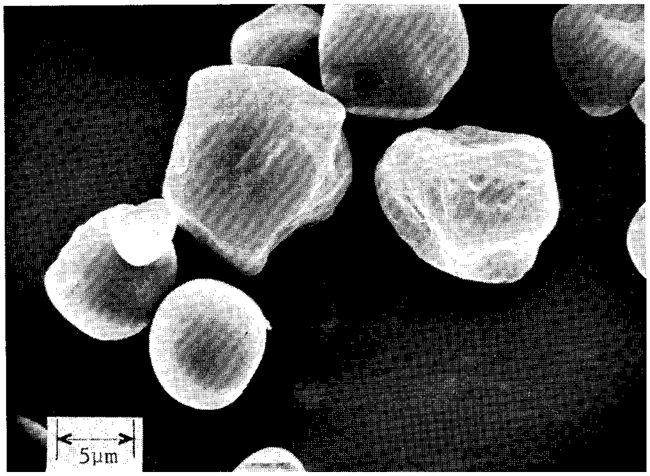
Table I: Pharmacopeial specifications for starch.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+(a)
Microbial limits	—	+	+
pH			
Corn starch	—	4.0–7.0(b)	4.0–7.0
Potato starch	—	5.0–8.0	5.0–8.0
Tapioca	—	—	4.5–7.0
Wheat starch	—	4.5–7.0	4.5–7.0
Acidity (rice starch)	—	+	—
Loss on drying			
Corn starch	⩽15.0%	⩽15.0%	⩽15.0%
Rice starch	⩽15.0%	⩽15.0%	—
Potato starch	⩽18.0%	⩽20.0%	⩽20.0%
Tapioca	—	—	⩽16.0%
Wheat starch	⩽15.0%	⩽15.0%	⩽15.0%
Residue on ignition	—	—	⩽0.6%(a)
Sulfated ash			
Corn starch	⩽0.5%	⩽0.6%	—
Rice starch	⩽1.0%	⩽1.0%	—
Potato starch	⩽0.5%	⩽0.6%	—
Wheat starch	⩽1.0%	⩽0.6%	—
Iron			
Corn starch	—	⩽10 ppm	⩽10 ppm
Potato starch	—	⩽10 ppm	⩽10 ppm
Tapioca starch	—	—	⩽0.002%
Wheat starch	—	⩽10 ppm	⩽10 ppm
Oxidizing substances			
Corn starch	—	⩽20 ppm	⩽20 ppm
Potato starch	—	⩽20 ppm	⩽20 ppm
Tapioca starch	—	—	⩽0.002%
Wheat starch	—	⩽20 ppm	⩽20 ppm
Sulfur dioxide			
Corn starch	—	⩽50 ppm	⩽50 ppm
Potato starch	—	⩽50 ppm	⩽50 ppm
Tapioca	—	—	⩽0.005%
Wheat starch	—	⩽50 ppm	⩽50 ppm
Total protein			
Corn starch	—	—	—
Rice starch	—	—	—
Potato starch	—	—	—
Wheat starch	—	⩽0.3%	—
Foreign matter	—	+	—

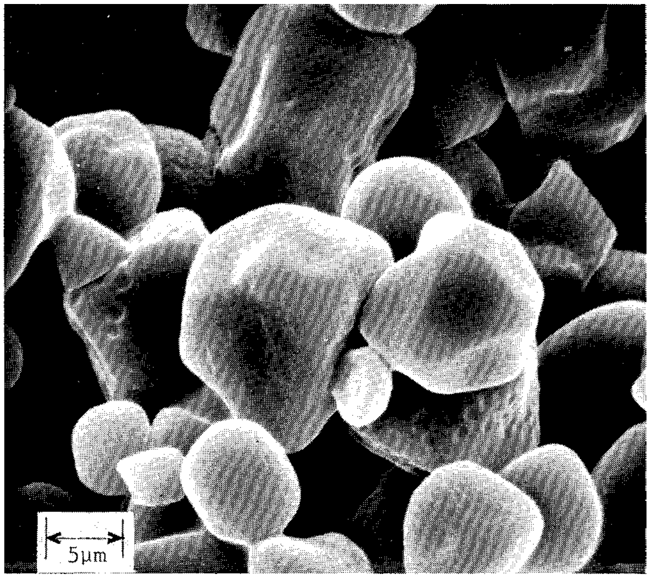
(a) *See* USPNF 23 Suppl 1.0.

(b) *See* PhEur 2005 Suppl 5.0.

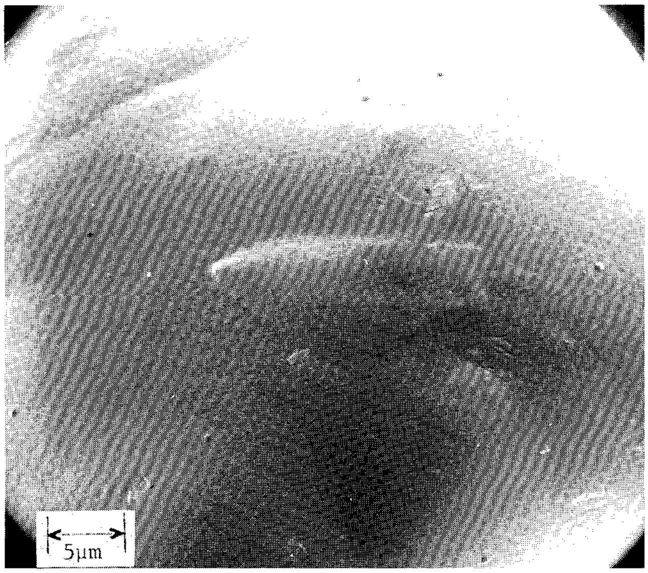
SEM: 1
Excipient: Corn starch
Manufacturer: Anheuser Busch
Lot No.: 96A-3 (67)
Magnification: 2400×
Voltage: 20 kV



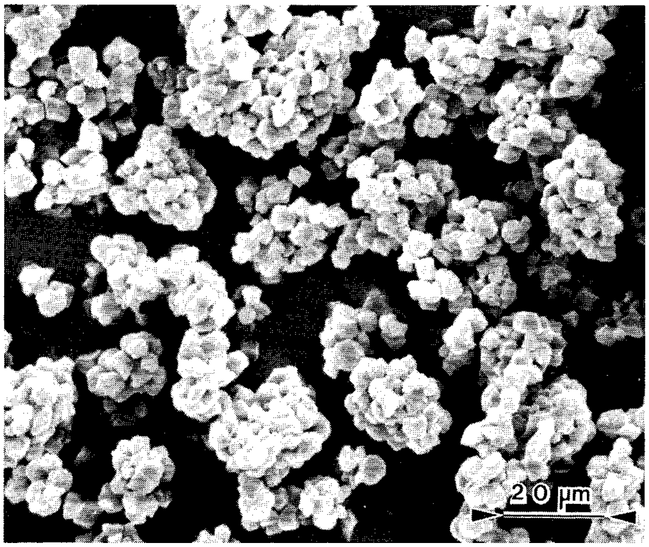
SEM: 2
Excipient: Corn starch
Manufacturer: AE Staley Mfg. Co.
Lot No.: 96A-4 (G77912)
Magnification: 2400×
Voltage: 20 kV



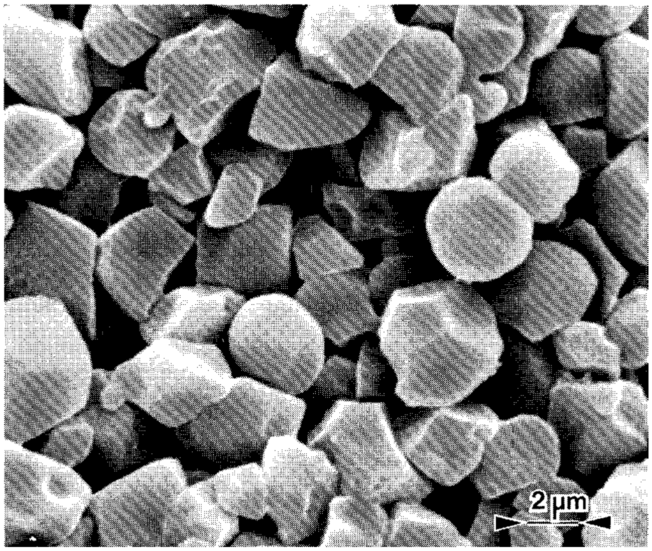
SEM: 3
Excipient: Potato starch
Manufacturer: Starchem
Lot No.: 96A-5 (1179)
Magnification: 2400×
Voltage: 20 kV



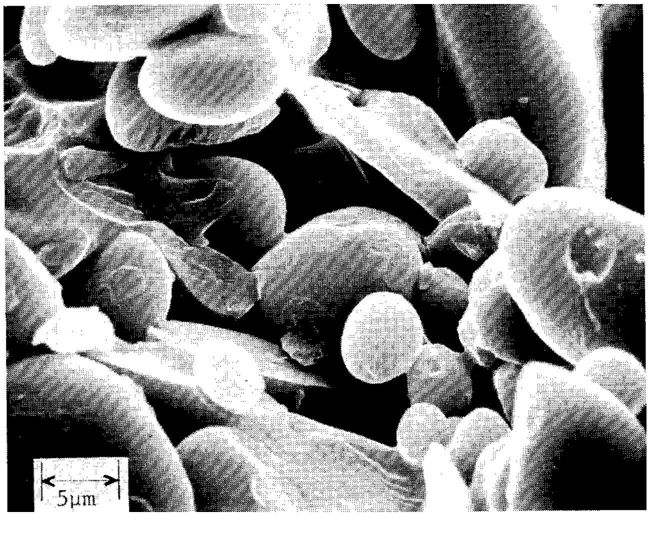
SEM: 4
Excipient: Rice starch
Supplier: Matheson, Coleman & Bell
Magnification: 600×



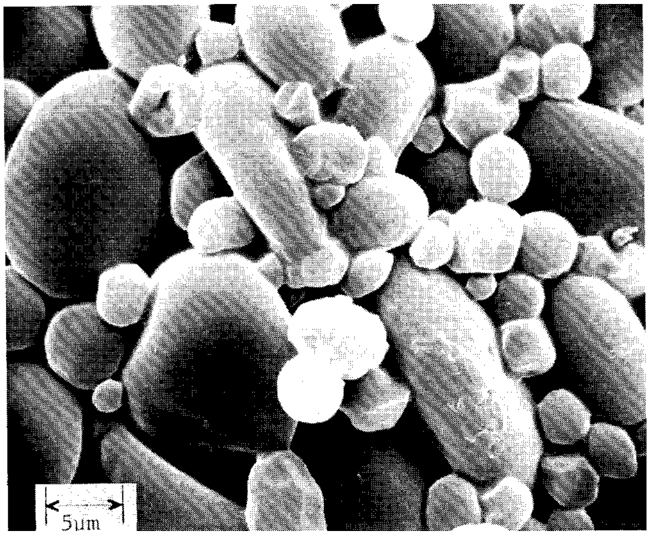
SEM: 5
Excipient: Rice starch
Supplier: Matheson, Coleman & Bell
Magnification: 3000×



SEM: 6
Excipient: Wheat starch (*Paygel 55*)
Manufacturer: Henkel Corp.
Lot No.: 96A-1 (2917D)
Magnification: 2400×
Voltage: 20 kV



SEM: 7
Excipient: Wheat starch (*Aytex P*)
Manufacturer: Henkel Corp.
Lot No.: 96A-2 (2919D)
Magnification: 2400×
Voltage: 20 kV



11 Stability and Storage Conditions

Dry, unheated starch is stable if protected from high humidity. When used as a diluent or disintegrant in solid-dosage forms, starch is considered to be inert under normal storage conditions. However, heated starch solutions or pastes are physically unstable and are readily attacked by microorganisms to form a wide variety of starch derivatives and modified starches that have unique physical properties.

Starch should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

—

13 Method of Manufacture

Starch is extracted from plant sources through a sequence of processing steps involving coarse milling, repeated water washing, wet sieving, and centrifugal separation. The wet starch obtained from these processes is dried and milled before use in pharmaceutical formulations.

14 Safety

Starch is widely used as an excipient in pharmaceutical formulations, particularly oral tablets.

Starch is an edible food substance and is generally regarded as an essentially nontoxic and nonirritant material.(23) However, oral consumption of massive doses can be harmful owing the formation of starch calculi, which cause bowel obstruction.(24) Starch may also cause granulomatous reactions when applied to the peritoneum or the meninges. Contamination of surgical wounds with the starch glove powder used by surgeons has also resulted in the development of granulomatous lesions.(25)

Allergic reactions to starch are extremely rare and individuals apparently allergic to one particular starch may not experience adverse effects with a starch from a different botanical source.

LD_{50} (mouse, IP): 6.6 g/kg(26)

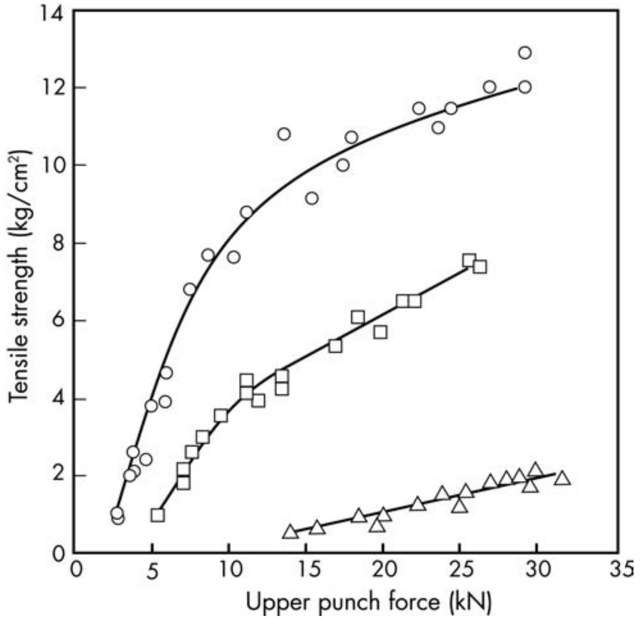


Figure 1: Compression characteristics of corn, potato and wheat starches.
□: Corn starch
○: Potato starch
△: Wheat starch
Tablet machine: Manesty F; speed: 50 per min; weight: 490–510 mg. Strength test: Diametral compression between flat-faced rams. Upper ram stationary, lower moving at 66 μm/s.

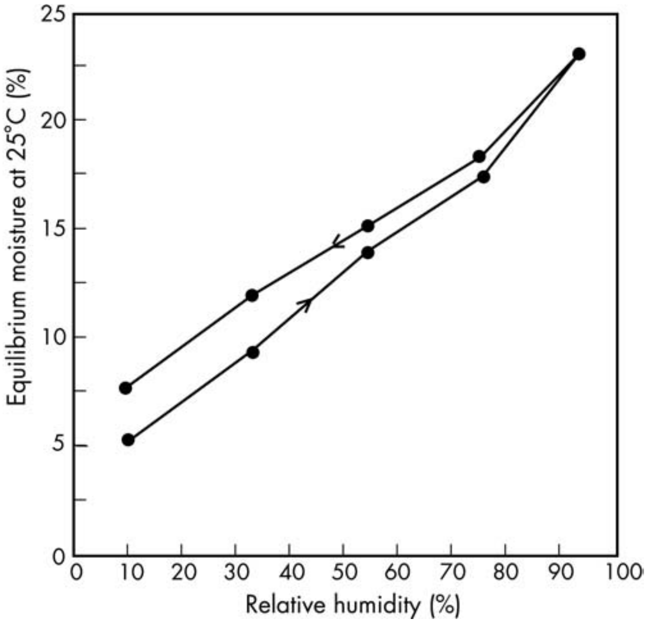


Figure 2: Sorption–desorption isotherm of corn starch. Anheuser Busch; Lot #67.

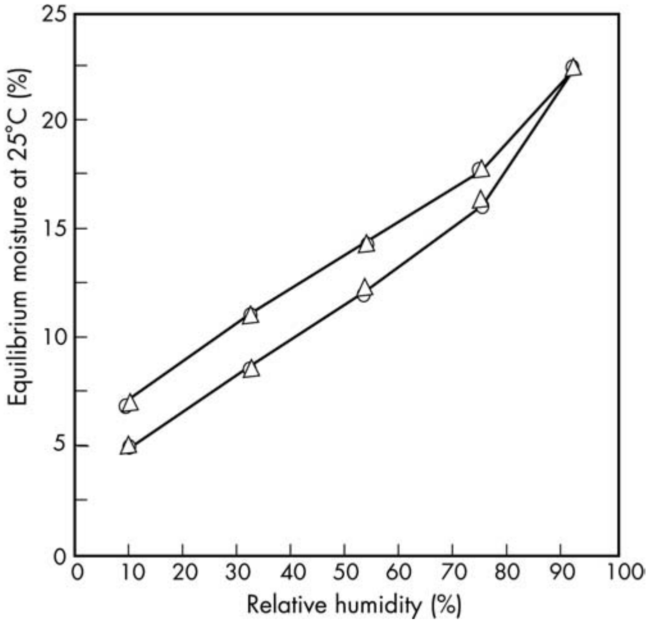


Figure 3: Sorption–desorption isotherm of wheat starch.
○: *Paygel 55* (Henkel Corp.; Lot #2917D)
△: *Aytex P* (Henkel Corp.; Lot #2919D)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosion.

In the UK, the long-term (8-hour TWA) occupational exposure limits for starch are 10 mg/m^3 for total inhalable dust and 4 mg/m^3 for respirable dust.(27)

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (buccal tablets, oral capsules, powders, suspensions and tablets; topical preparations; and vaginal tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Amylopectin; α-amylose; maltodextrin; starch, pregelatinized; starch, sterilizable maize.

Amylopectin

CAS number: [9037-22-3]

Comments: amylopectin is a branched D-glucan with mostly α-D-(1→4) and approximately 4% α-D-(1→6) linkages.

The EINECS number for amylopectin is 232-911-6.

α-Amylose

CAS number: [9005-82-7]

Comments: amylose is a linear (1→4)-α-D-glucan.

18 Comments

Note that corn starch is also known as maize starch and that tapioca starch is also known as cassava starch.

Whereas the USPNF 23 specifies that starch should be produced from corn, potato, tapioca, or wheat, the BP 2004 also permits starch to be produced from rice. In tropical and subtropical countries where these starches may not be readily available, the BP 2004 additionally permits the use of tapioca starch, subject to additional requirements.

Starches from different plant sources differ in their amylose/amylopectin ratio. For example, corn starch contains about 27% amylose, potato starch about 22%, and tapioca starch about 17%. In contrast, waxy corn starch contains almost entirely amylopectin, with no amylose. These differences modify the physical properties of the starches such that the various types may not be interchangeable in a given pharmaceutical application. For example, amylose-rich maize starch has been studied as a potential tablet film-coating ingredient.(28)

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20 General References

—

21 Authors

LY Galichet.

22 Date of Revision

25 August 2005.

Starch, Pregelatinized

1 Nonproprietary Names

BP: Pregelatinised starch
PhEur: Amylum pregelificatum
USPNF: Pregelatinized starch

2 Synonyms

Compressible starch; *Instastarch*; *Lycatab C*; *Lycatab PGS*; *Merigel*; *National 78-1551*; *Pharma-Gel*; *Prejel*; *Sepistab ST 200*; *Spress B820*; *Starch 1500 G*; *Tablitz*; *Unipure LD*; *Unipure WG220*.

3 Chemical Name and CAS Registry Number

Pregelatinized starch [9005-25-8]

4 Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ where n = 300–1000.

Pregelatinized starch is a starch that has been chemically and/or mechanically processed to rupture all or part of the starch granules and so render the starch flowable and directly compressible. Partially pregelatinized grades are also commercially available. Typically, pregelatinized starch contains 5% of free amylose, 15% of free amylopectin, and 80% unmodified starch. The USPNF 23 does not specify the botanical origin of the original starch, but the PhEur 2005 specifies that pregelatinized starch is obtained from maize (corn), potato, or rice starch. *See also* Starch and Section 13.

5 Structural Formula

See Starch.

6 Functional Category

Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent,(1,2) and disintegrant.(3)

In comparison to starch, grades of pregelatinized starch may be produced with enhanced flow and compression characteristics such that the pregelatinized material may be used as a tablet binder in dry-compression or direct compression processes.(4–14) In such processes, pregelatinized starch is self-lubricating. However, when it is used with other excipients it may be necessary to add a lubricant to a formulation. Although magnesium stearate 0.25% w/w is commonly used for this purpose, concentrations greater than this may have adverse effects on tablet strength and dissolution. Therefore, stearic acid is generally the preferred lubricant with pregelatinized starch.(15)

Pregelatinized starch may also be used in wet granulation processes.(16) *See* Table I.

Table I: Uses of pregelatinized starch.

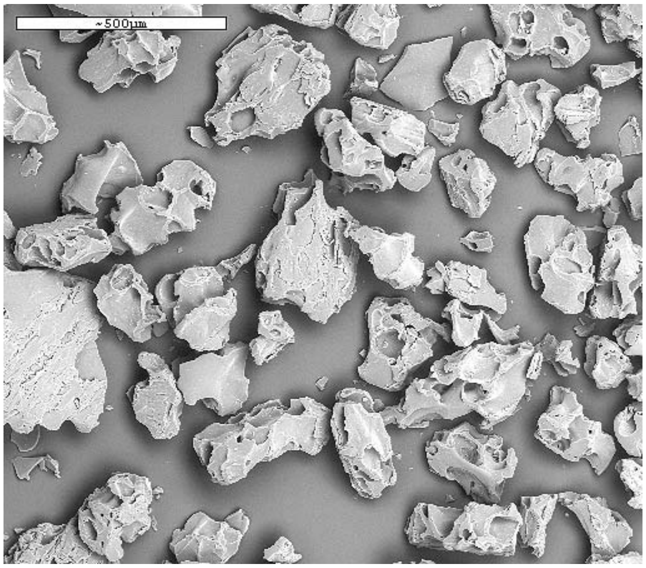
Use	Concentration (%)
Diluent (hard gelatin capsules)	5–75
Tablet binder (direct compression)	5–20
Tablet binder (wet granulation)	5–10
Tablet disintegrant	5–10

8 Description

Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste.

Examination of fully pregelatinized starch as a slurry in cold water, under a polarizing microscope, reveals no significant ungelatinized granules, i.e., no 'maltese crosses' characteristic of the starch birefringence pattern. Examination of samples suspended in glycerin shows characteristic forms depending upon the method of drying used during manufacture: either irregular chunks from drum drying or thin plates. Partially pregelatinized starch (e.g., *Starch 1500G* and *Sepistab ST200*) show retention of birefringence patterns typical of unmodified starch granules.

SEM: 1
Excipient: Lycatab PGS
Manufacturer: Roquette Frères



9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for pregelatinized starch.

Test	PhEur 2005	USPNF 23
Identification	+	+
pH (10% w/v slurry)	4.5–7.0	4.5–7.0
Iron	⩽20 ppm	⩽0.002%
Oxidizing substances	+	+
Sulfur dioxide	⩽50 ppm	⩽0.008%
Microbial limits	+	+
Loss on drying	⩽15.0%	⩽14.0%
Residue on ignition	—	⩽0.5%
Foreign matter	+	—
Sulfated ash	⩽0.6%	—
Organic volatile impurities	—	+

10 Typical Properties

Acidity/alkalinity: pH = 4.5–7.0 for a 10% w/v aqueous dispersion.

Angle of repose: 40.7° (6)

Compressibility: *see* Starch.

Density (bulk): 0.586 g/cm^3

Density (tapped): 0.879 g/cm^3

Density (true): 1.516 g/cm^3

Flowability: 18–23% (Carr compressibility index)(17)

Moisture content: pregelatinized maize starch is hygroscopic.(14,18,19) *See also* Figure 1.

Particle size distribution: 30–150 μm, median diameter 52 μm. For partially pregelatinized starch, greater than 90% through a US #100 mesh (149 μm); and less than 0.5% retained on a US #40 mesh (420 μm).

Solubility: practically insoluble in organic solvents. Slightly soluble to soluble in cold water, depending upon the degree of pregelatinization. Pastes can be prepared by sifting the pregelatinized starch into stirred, cold water. Cold-water-soluble matter for partially pregelatinized starch is 10–20%.

Specific surface area:
0.26 m^2/g (Colorcon);
0.18–0.28 m^2/g (Roquette Ltd).

Viscosity (dynamic): 8–10 mPa s (8–10 cP) for a 2% w/v aqueous dispersion at 25°C.

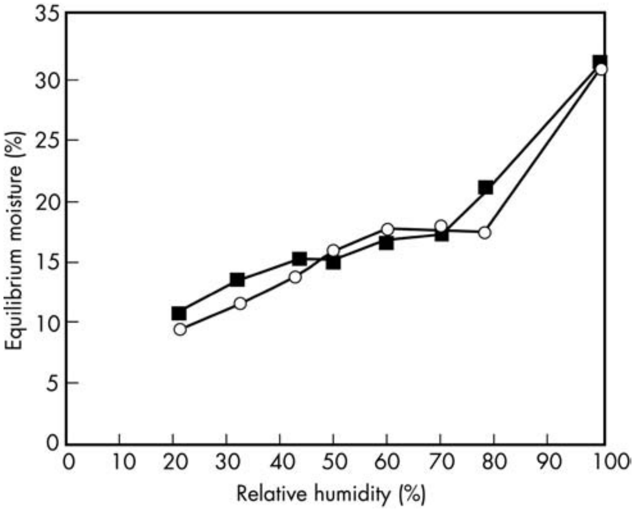


Figure 1: Pregelatinized starch sorption–desorption isotherm.
○: Sorption
■: Desorption.

11 Stability and Storage Conditions

Pregelatinized starch is a stable but hygroscopic material, which should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

—

13 Method of Manufacture

Food-grade pregelatinized starches are prepared by heating an aqueous slurry containing up to 42% w/w of starch at 62–72°C. Chemical additives that may be included in the slurry are gelatinization aids (salts or bases) and surfactants, added to control rehydration or minimize stickiness during drying. After heating, the slurry may be spray-dried, roll-dried, extruded, or drum-dried. In the last case, the dried material may be processed to produce a desired particle size range.

Pharmaceutical grades of fully pregelatinized starch use no additives and are prepared by spreading an aqueous suspension of ungelatinized starch on hot drums where gelatinization and subsequent drying takes place. Partially pregelatinized starch is produced by subjecting moistened starch to mechanical pressure. The resultant material is ground and the moisture content is adjusted to specifications.

14 Safety

Pregelatinized starch and starch are widely used in oral solid-dosage formulations. Pregelatinized starch is generally regarded as a nontoxic and nonirritant excipient. However, oral consumption of large amounts of pregelatinized starch may be harmful.

See Starch for further information.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosions.

In the UK, the long-term (8-hour TWA) occupational exposure limits for starch are 10 mg/m^3 for total inhalable dust and 4 mg/m^3 for respirable dust.(20)

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules, suspensions, and tablets; vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Starch; starch, sterilizable maize.

18 Comments

A low-moisture grade of pregelatinized starch, *Starch 1500 LM* (Colorcon), containing less than 7% of water, specifically intended for use as a diluent in capsule formulations is commercially available.(15)

Sepistab ST200 is described as an agglomerate of starch granules consisting of native and pregelatinized corn starch.(21) Compression characteristics of pregelatinized starches from sorghum and plantain have been evaluated against traditional corn-based products.(22)

19 Specific References

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21 Authors

AH Kibbe.

22 Date of Revision

17 August 2005.

Starch, Sterilizable Maize

1 Nonproprietary Names

USP: Absorbable dusting powder

2 Synonyms

Bio-sorb; double-dressed, white maize starch; *Fluidamid R444P*; *Keoflo ADP*; *Meritena*; modified starch dusting powder; *Pure-Dent B851*; starch-derivative dusting powder; sterilizable corn starch.

3 Chemical Name and CAS Registry Number

Sterilizable maize starch

4 Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ where n = 300–1000.

Sterilizable maize starch is a modified corn (maize) starch that may also contain up to 2.0% of magnesium oxide.

See also Starch.

5 Structural Formula

See Starch.

6 Functional Category

Lubricant for surgeons' and examination gloves; vehicle for medicated dusting powders.

7 Applications in Pharmaceutical Formulation or Technology

Sterilizable maize starch is a chemically or physically modified corn (maize) starch that does not gelatinize on exposure to moisture or steam sterilization. Sterilizable maize starch is primarily used as a lubricant for examination and surgeons' gloves although because of safety concerns unlubricated gloves are now generally recommended. It is also used as a vehicle for medicated dusting powders.

8 Description

Sterilizable maize starch occurs as an odorless, white, free-flowing powder. Particles may be rounded or polyhedral in shape.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sterilizable maize starch.

Test	USP 28
Identification	+
Stability to autoclaving	+
Sedimentation	+
pH (1 in 10 suspension)	10.0–10.8
Loss on drying	⩽12%
Residue on ignition	⩽3.0%
Magnesium oxide	⩽2.0%
Heavy metals	⩽0.001%

10 Typical Properties

Acidity/alkalinity: pH = 9.5–10.8 for a 10% w/v suspension at 25°C.

Density: 1.48 g/cm^3

Density (bulk): 0.47–0.59 g/cm^3

Density (tapped): 0.64–0.83 g/cm^3

Flowability: 24–30% (Carr compressibility index)(1)

Moisture content: 10–15%

Particle size distribution: 6–25 μm; median diameter is 16 μm.

Solubility: very slightly soluble in chloroform and ethanol (95%); practically insoluble in water.

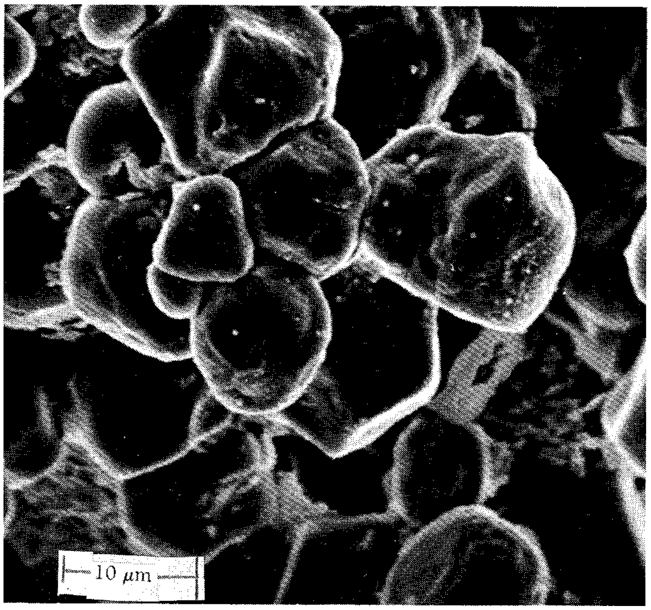
Specific surface area: 0.50–1.15 m^2/g

11 Stability and Storage Conditions

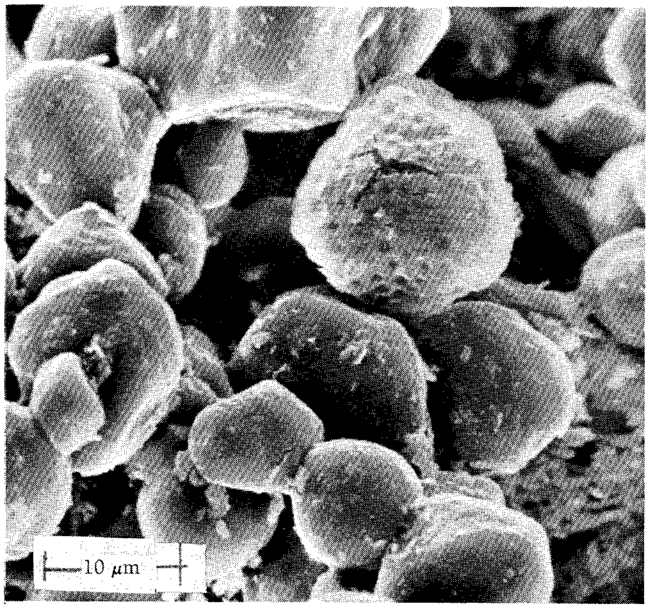
Sterilizable maize starch may be sterilized by autoclaving at 121°C for 20 minutes, by ethylene oxide, or by irradiation.(2)

Sterilizable maize starch should be stored in a well-closed container in a cool, dry place.

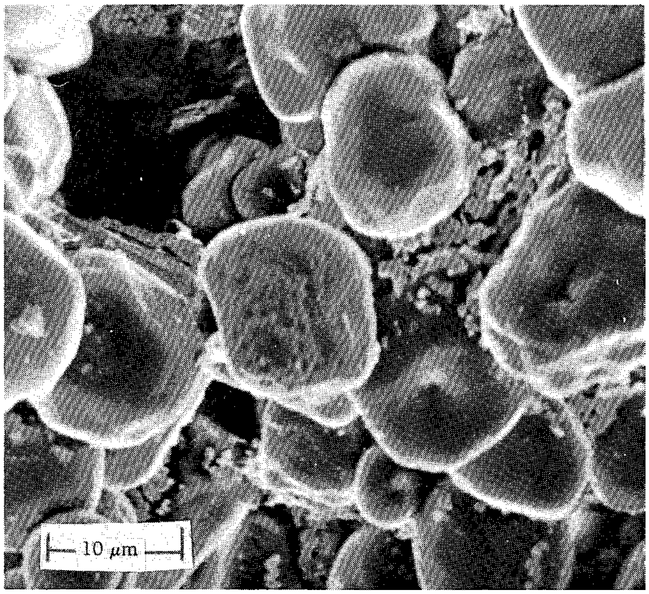
SEM: 1
Excipient: Sterilizable maize starch
Manufacturer: Corn Products
Magnification: 2000×



SEM: 2
Excipient: Sterilizable maize starch
Manufacturer: Biosorb
Magnification: 2000×



SEM: 3
Excipient: Sterilizable maize starch
Manufacturer: J & W Starches Ltd
Magnification: 2000×



12 Incompatibilities

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13 Method of Manufacture

Corn starch (maize starch) is physically or chemically modified by treatment with either phosphorus oxychloride or epichlorhydrin so that the branched-chain and straight-chain starch polymers crosslink. Up to 2.0% of magnesium oxide may also be added to the starch.

See also Starch.

14 Safety

Sterilizable maize starch is primarily used as a lubricant for surgeons' gloves and as a vehicle for topically applied dusting powders.

Granulomatous reactions and peritonitis at operation sites have been attributed to contamination with surgical glove powders containing sterilizable maize starch.(3–8) The use of excessive quantities of sterilizable maize starch on surgeons' gloves should therefore be avoided.

See also Starch.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosions.

In the UK, the long-term (8-hour TWA) occupational exposure limits for starch are 10 mg/m^3 for total inhalable dust and 4 mg/m^3 for respirable dust.(9)

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral tablets and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Starch; starch, pregelatinized.

18 Comments

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19 Specific References

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20 General References

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21 Authors

PJ Weller.

22 Date of Revision

13 April 2005.

Stearic Acid

1 Nonproprietary Names

BP: Stearic acid
JP: Stearic acid
PhEur: Acidum stearicum
USPNF: Stearic acid

2 Synonyms

Cetylacetic acid; *Crodacid*; E570; *Edenor*; *Emersol*; *Hystrene*; *Industrene*; *Kortacid 1895*; *Pearl Steric*; *Pristerene*; stereophanic acid; *Tegostearic.*

3 Chemical Name and CAS Registry Number

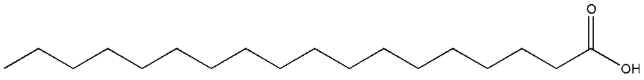
Octadecanoic acid [57-11-4]

4 Empirical Formula and Molecular Weight

$C_{18}H_{36}O_2$ 284.47 (for pure material)

The USPNF 23 describe stearic acid as a mixture of stearic acid ($C_{18}H_{36}O_2$) and palmitic acid ($C_{16}H_{32}O_2$). In the USPNF 23, the content of stearic acid is not less than 40.0% and the sum of the two acids is not less than 90.0%. The USPNF 23 also contains a monograph for purified stearic acid; *see* Section 17. The PhEur 2005 contains a single monograph for stearic acid but defines stearic acid 50, stearic acid 70, and stearic acid 95 as containing specific amounts of stearic acid ($C_{18}H_{36}O_2$); *see* Section 9.

5 Structural Formula



6 Functional Category

Emulsifying agent; solubilizing agent; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

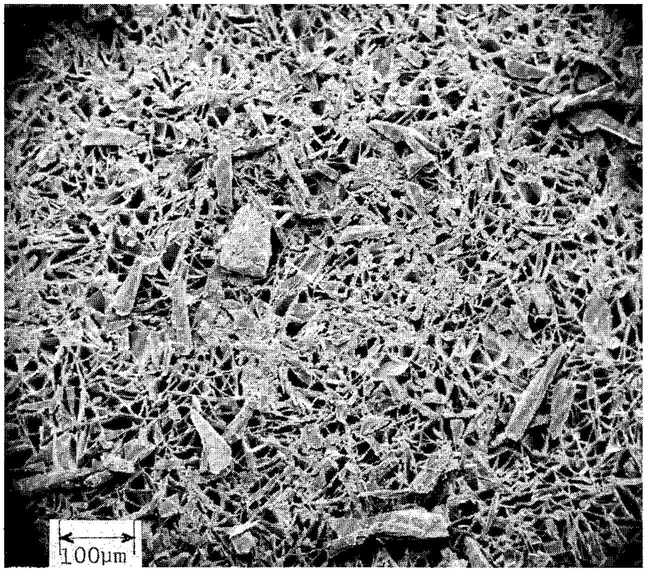
Stearic acid is widely used in oral and topical pharmaceutical formulations. It is mainly used in oral formulations as a tablet and capsule lubricant;(1–3) *see* Table I, although it may also be used as a binder(4) or in combination with shellac as a tablet coating. It has also been suggested that stearic acid may be used as a sustained-release drug carrier.(5)

In topical formulations, stearic acid is used as an emulsifying and solubilizing agent. When partially neutralized with alkalis or triethanolamine, stearic acid is used in the preparation of creams.(6,7) The partially neutralized stearic acid forms a creamy base when mixed with 5–15 times its own weight of aqueous liquid; the appearance and plasticity of the cream being determined by the proportion of alkali used.

Stearic acid is used as the hardening agent in glycerin suppositories.

Stearic acid is also widely used in cosmetics and food products.

SEM: 1
Excipient: Stearic acid, 95% (*Emersol 153*)
Manufacturer: Emery Industries
Lot No.: 18895
Magnification: 120×
Voltage: 10 kV



SEM: 2
Excipient: Stearic acid, food grade (*Emersol 6332*)
Manufacturer: Emery Industries
Lot No.: 18895
Magnification: 120×
Voltage: 10 kV

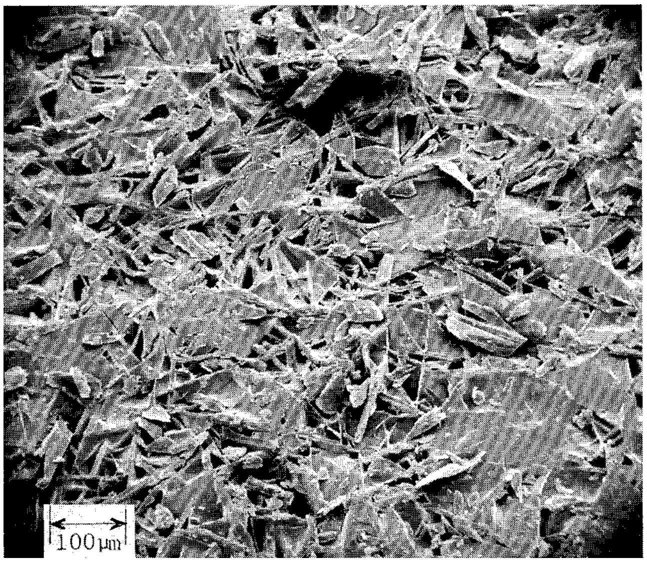


Table I: Uses of stearic acid.

Use	Concentration (%)
Ointments and creams	1–20
Tablet lubricant	1–3

8 Description

Stearic acid is a hard, white or faintly yellow-colored, somewhat glossy, crystalline solid or a white or yellowish white powder. It has a slight odor and taste suggesting tallow.

See also Section 13.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for stearic acid.

Test	JP 2001	PhEur 2005	USPNF 23
Acidity	—	+	—
Acid value	194–210	194–212	—
Appearance	—	+	—
Characters	—	+	—
Content of stearic acid	—	—	$\geqslant$40.0%
Stearic acid 50	—	40–60%	—
Stearic acid 70	—	60–80%	—
Stearic acid 95	—	$\geqslant$90.0%	—
Content of stearic and palmitic acids	—	—	$\geqslant$90.0%
Stearic acid 50	—	$\geqslant$90.0%	—
Stearic acid 70	—	$\geqslant$90.0%	—
Stearic acid 95	—	$\geqslant$96.0%	—
Congealing temperature	56.0–72.0°C	—	$\geqslant$54°C
Freezing point		+	
Stearic acid 50	—	53–59°C	—
Stearic acid 70	—	57–64°C	—
Stearic acid 95	—	64–69°C	—
Iodine value	$\leqslant$4.0	+	$\leqslant$4.0
Stearic acid 50	—	$\leqslant$4.0%	—
Stearic acid 70	—	$\leqslant$4.0%	—
Stearic acid 95	—	$\leqslant$1.5%	—
Nickel	—	$\leqslant$1 ppm	—
Residue on ignition	$\leqslant$0.1%	—	$\leqslant$0.1%
Heavy metals	$\leqslant$20 ppm	—	$\leqslant$0.001%
Neutral fat or paraffin	+	—	+
Mineral acid	+	—	+
Organic volatile impurities	—	—	+

10 Typical Properties

Acid value: 200–212
Density (bulk): $\approx$0.537 g/cm^3
Density (tapped): 0.571 g/cm^3
Density (true): 0.980 g/cm^3
Melting point: $\geqslant$54°C
Moisture content: contains practically no water.
Saponification value: 200–220
Solubility: freely soluble in benzene, carbon tetrachloride, chloroform, and ether; soluble in ethanol (95%), hexane, and propylene glycol; practically insoluble in water.(8)
Specific surface area: 0.51–0.53 m^2/g

See also Section 17 and Table III.

11 Stability and Storage Conditions

Stearic acid is a stable material; an antioxidant may also be added to it; *see* Section 13. The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Stearic acid is incompatible with most metal hydroxides and may be incompatible with oxidizing agents.

Insoluble stearates are formed with many metals; ointment bases made with stearic acid may show evidence of drying out or lumpiness due to such a reaction when compounded with zinc or calcium salts.

A number of differential scanning calorimetry studies have investigated the compatibility of stearic acid with drugs. Although such laboratory studies have suggested incompatibilities, e.g. with naproxen,(9) they may not necessarily be applicable to formulated products.

Stearic acid has been reported to cause pitting in the film coating of tablets coated using an aqueous film-coating technique; the pitting was found to be a function of the melting point of the stearic acid.(10)

13 Method of Manufacture

Stearic acid is manufactured by hydrolysis of fat by continuous exposure to a countercurrent stream of high-temperature water and fat in a high-pressure chamber. The resultant mixture is purified by vacuum steam distillation and the distillates are then separated using selective solvents.

Stearic acid may also be manufactured by the hydrogenation of cottonseed and other vegetable oils; by the hydrogenation and subsequent saponification of olein followed by recrystallization from alcohol; and from edible fats and oils by boiling with sodium hydroxide, separating any glycerin, and decomposing the resulting soap with sulfuric or hydrochloric acid. The stearic acid is then subsequently separated from any oleic acid by cold expression.

Stearic acid is derived from edible fat sources unless it is intended for external use, in which case nonedible fat sources may be used. The USPNF 23 states that stearic acid labeled solely for external use is exempt from the requirement that it be prepared from edible sources. Stearic acid may contain a suitable antioxidant such as 0.005% w/w butylated hydroxytoluene.

14 Safety

Stearic acid is widely used in oral and topical pharmaceutical formulations; it is also used in cosmetics and food products. Stearic acid is generally regarded as a nontoxic and nonirritant material. However, consumption of excessive amounts may be harmful.

LD_{50} (mouse, IV): 23 mg/kg(11)
LD_{50} (rat, IV): 21.5 mg/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Stearic acid dust may be irritant to the skin, eyes, and mucous membranes. Eye protection, gloves, and a dust respirator are recommended. Stearic acid is combustible.

Table III: Specifications of different stearic acid grades.

Product	Stearic acid content (%)	Melting range (°C)	Acid value	Iodine value	Saponification value	Unsaponifiable matter (%)
Hystrene 5016	44	54.5–56.5	206–210	$\leqslant$0.5	206–211	$\leqslant$0.2
Hystrene 7018	68.5	61.0–62.5	200–205	$\leqslant$0.5	200–206	$\leqslant$0.2
Hystrene 9718	90	66.5–68.0	196–201	$\leqslant$0.8	196–202	$\leqslant$0.3
Industrene 7018	65	58.0–62.0	200–207	$\leqslant$1.5	200–208	$\leqslant$0.5
Industrene 8718	87	64.5–67.5	196–201	$\leqslant$2.0	196–202	$\leqslant$1.5

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe (fatty acids). Included in the FDA Inactive Ingredients Guide (sublingual tablets; oral capsules, solutions, suspensions, and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Calcium stearate; magnesium stearate; polyoxyethylene stearates; purified stearic acid; zinc stearate.

Purified stearic acid

Empirical formula: $C_{18}H_{36}O_2$
Molecular weight: 284.47
CAS number: [57-11-4]
Synonyms: octadecanoic acid.
Acid value: 195–200
Boiling point: 361°C
Density: 0.847 g/cm^3 at 70°C
Flash point: 196°C
Iodine number: $\leqslant$1.5
Melting point: 66–69°C
Refractive index: $n_D^{80} = 1.4299$
Solubility: soluble 1 in 5 parts benzene, 1 in 6 parts carbon tetrachloride, 1 in 2 parts chloroform, 1 in 15 parts ethanol, 1 in 3 parts ether; practically insoluble in water.
Vapor density (relative): 9.80 (air = 1)
Comments: The USPNF 23 describes purified stearic acid as a mixture of stearic acid ($C_{18}H_{36}O_2$) and palmitic acid ($C_{16}H_{32}O_2$), which together constitute not less than 96.0% of the total content. The content of $C_{18}H_{36}O_2$ is no less than 90.0% of the total.

18 Comments

A wide range of different grades of stearic acid are commercially available that have varying chemical compositions and hence different physical and chemical properties; *see* Table III.(12) A specification for stearic acid is contained in the Food Chemicals Codex (FCC).

The EINECS number for stearic acid is 200-313-4.

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21 Authors

LV Allen.

22 Date of Revision

9 August 2005.

Stearyl Alcohol

1 Nonproprietary Names

BP: Stearyl alcohol
JP: Stearyl alcohol
PhEur: Alcohol stearylicus
USPNF: Stearyl alcohol

2 Synonyms

Cachalot; *Crodacol S95*; *Hyfatol 18-95*; *Hyfatol 18-98*; *Lanette 18*; *Lipocol S*; *Lipocol S-DEO*; *n*-octadecanol; octadecyl alcohol; *Rita SA*; *Stearol*; *Stenol*; *Tego Alkanol 18*.

3 Chemical Name and CAS Registry Number

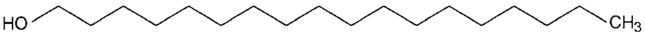
1-Octadecanol [112-92-5]

4 Empirical Formula and Molecular Weight

$C_{18}H_{38}O$ 270.48 (for pure material)

The PhEur 2005 describes stearyl alcohol as a mixture of solid alcohols containing not less than 95% of 1-octadecanol, $C_{18}H_{38}O$. The USPNF 23 states that stearyl alcohol contains not less than 90% of 1-octadecanol, the remainder consisting chiefly of related alcohols.

5 Structural Formula



6 Functional Category

Stiffening agent.

7 Applications in Pharmaceutical Formulation or Technology

Stearyl alcohol is used in cosmetics(1,2) and topical pharmaceutical creams and ointments as a stiffening agent. By increasing the viscosity of an emulsion, stearyl alcohol increases its stability. Stearyl alcohol also has some emollient and weak emulsifying properties and is used to increase the water-holding capacity of ointments, e.g. petrolatum. In addition, stearyl alcohol has been used in controlled-release tablets,(3,4) suppositories,(5,6) and microspheres.(7,8) It has also been investigated for use as a transdermal penetration enhancer.(9)

8 Description

Stearyl alcohol occurs as hard, white, waxy pieces, flakes, or granules with a slight characteristic odor and bland taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for stearyl alcohol.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	—	+	+
Characters	—	+	—
Appearance of solution	+	+	—
Melting range	56–62°C	57–60°C	55–60°C
Acid value	⩽1.0	⩽1.0	⩽2.0
Iodine value	⩽2.0	⩽2.0	⩽2.0
Hydroxyl value	200–220	197–217	195–220
Saponification value	—	⩽2.0	—
Ester value	⩽3.0	—	—
Residue on ignition	⩽0.05%	—	—
Assay (of $C_{18}H_{38}O$)	—	⩾95%	⩾90.0%

10 Typical Properties

Autoignition temperature: 450°C
Boiling point: 210.5°C at 2 kPa (15 mmHg)
Density (true): 0.884–0.906 g/cm^3(10)
Flash point: 191°C (open cup)
Freezing point: 55–57°C
Melting point: 59.4–59.8°C for the pure material.
Refractive index: n_D^{60} = 1.4388 at 60°C
Solubility: soluble in chloroform, ethanol (95%), ether, hexane, propylene glycol, and vegetable oils; practically insoluble in water.
Vapor pressure: 133.3 Pa (1 mmHg) at 150.3°C
Viscosity (dynamic): 9.82 mPa s at 64°C(10)

11 Stability and Storage Conditions

Stearyl alcohol is stable to acids and alkalis and does not usually become rancid. It should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatible with strong oxidizing agents and strong acids.

13 Method of Manufacture

Historically, stearyl alcohol was prepared from sperm whale oil but is now largely prepared synthetically by reduction of ethyl stearate with lithium aluminum hydride.

14 Safety

Stearyl alcohol is generally considered to be an innocuous, nontoxic material. However, adverse reactions to stearyl alcohol present in topical preparations have been reported. These include contact urticaria and hypersensitivity reactions, which are possibly due to impurities contained in stearyl alcohol rather than stearyl alcohol itself.(11–15)

The probable lethal oral human dose is greater than 15 g/kg.

LD_{50} (rat, oral): 20 g/kg(16)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Stearyl alcohol is not a fire hazard, although it will burn and may give off noxious fumes containing carbon monoxide.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral tablets, rectal topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Cetostearyl alcohol; cetyl alcohol.

18 Comments

The EINECS number for stearyl alcohol is 204-017-6.

19 Specific References

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21 Authors

RT Guest.

22 Date of Revision

23 August 2005.

Sucralose

1 Nonproprietary Names

USPNF: Sucralose

2 Synonyms

Splenda; TGS; 1′,4′,6′-trichlorogalactosucrose; 4,1′,6′-trichloro-4,1′,6′-trideoxy-*galacto*-sucrose.

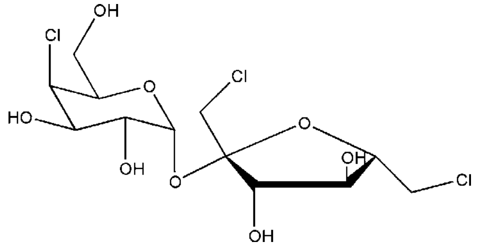
3 Chemical Name and CAS Registry Number

1,6-Dichloro-1,6-dideoxy-β-D-fructofuranosyl-4-chloro-4-deoxy-α-D-galactopyranoside [56038-13-2]

4 Empirical Formula and Molecular Weight

$C_{12}H_{19}Cl_3O_8$ 397.64

5 Structural Formula



6 Functional Category

Sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

Sucralose is used as a sweetening agent in beverages, foods, and pharmaceutical applications. It has a sweetening power approximately 300–1000 times that of sucrose and has no aftertaste. It has no nutritional value, is noncariogenic, and produces no glycemic response. *See also* Table I.

Table I: Uses of sucralose.

Use	Concentration (%)
Food products	0.03–0.24

8 Description

Sucralose is a white to off-white colored, free-flowing, crystalline powder.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for sucralose.

Test	USPNF 23
Identification	+
Specific rotation	+84.0° to +87.5°
Water	⩽2.0%
Residue on ignition	⩽0.7%
Heavy metals	⩽0.001%
Limit of hydrolysis products	⩽0.1%
Limit of methanol	⩽0.1%
Related compounds	⩽0.5%
Assay (dried basis)	98.0–102.0%

10 Typical Properties

Acidity/alkalinity: pH = 5–6 (10% w/v aqueous solution at 20°C)

Density (bulk): 0.35 g/cm^3

Density (tapped): 0.62 g/cm^3

Density (true): 1.63 g/cm^3

Melting point: 130°C (for anhydrous crystalline form); 36.5°C (for pentahydrate).

Particle size distribution: 90% < 12 μm in size.

Partition coefficient: $\log_{10} P$ = —0.51 (octanol:water)

Refractive index: 1.33 to 1.37

Solubility: freely soluble in ethanol (95%), methanol, and water; slightly soluble in ethyl acetate.

Specific rotation $[\alpha]_D^{20}$**:** +84.0° to +87.5° (1% w/v aqueous solution); +68.2° (1.1% w/v solution in ethanol).

Viscosity: 0.6–3.8 mPa s

11 Stability and Storage Conditions

Sucralose is a relatively stable material. In aqueous solution, at highly acidic conditions (pH < 3), and at high temperatures (⩽35°C), it is hydrolyzed to a limited extent, producing 4-chloro-4-deoxygalactose and 1,6-dichloro-1,6-dideoxyfructose. In food products, sucralose remains stable throughout extended storage periods, even at low pH. However, it is most stable at pH 5–6.

Sucralose should be stored in a well-closed container in a cool, dry place, at a temperature not exceeding 21°C. Sucralose, when heated at elevated temperatures, may break down with the release of carbon dioxide, carbon monoxide, and minor amounts of hydrogen chloride.

12 Incompatibilities

—

13 Method of Manufacture

Sucralose may be prepared by a variety of methods that involve the selective substitution of three sucrose hydroxyl groups by chlorine. Sucralose can also be synthesized by the reaction of sucrose (or an acetate) with thionyl chloride.

14 Safety

Sucralose is generally regarded as a nontoxic and nonirritant material and is approved, in a number of countries, for use in food products. Following oral consumption, sucralose is mainly unabsorbed and is excreted in the feces.(1–3)

The WHO has set an acceptable daily intake for sucralose of up to 15 mg/kg body-weight.(4)

LD_{50} (mouse, oral): > 16 g/kg
LD_{50} (rat, oral): > 10 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

The FDA, in April 1998, approved sucralose for use as a tabletop sweetener and as an additive in a variety of food products. In the UK, sucralose was authorized for use in food products on a 2-year temporary basis in March 2002.(5) It is also accepted for use in many other countries worldwide. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Sucrose.

18 Comments

The sweetening effect of sucralose is not reduced by heating and food products containing sucralose may be subjected to high-temperature processes such as pasteurization, sterilization, UHT processing and baking. Sucralose is often blended with maltodextrin or dextrose as bulking agents in its granular form.

A specification for sucralose is contained in the Food Chemicals Codex (FCC).

19 Specific References

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21 Authors

BA Langdon, MP Mullarney.

22 Date of Revision

26 August 2005.

Sucrose

1 Nonproprietary Names

BP: Sucrose
JP: Sucrose
PhEur: Saccharum
USPNF: Sucrose

2 Synonyms

Beet sugar; cane sugar; α-D-glucopyranosyl-β-D-fructofuranoside; refined sugar; saccharose; sugar.

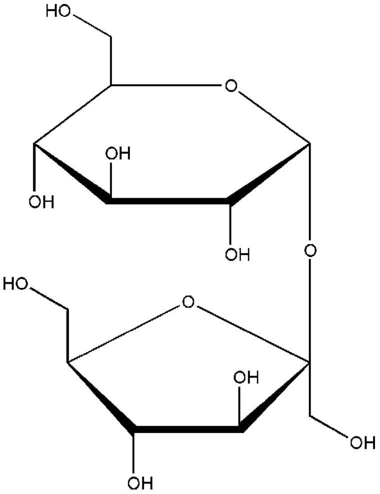
3 Chemical Name and CAS Registry Number

β-D-fructofuranosyl-α-D-glucopyranoside [57-50-1]

4 Empirical Formula and Molecular Weight

$C_{12}H_{22}O_{11}$ 342.30

5 Structural Formula



6 Functional Category

Base for medicated confectionery; coating agent; granulating agent; sugar coating adjunct; suspending agent; sweetening agent; tablet binder; tablet and capsule diluent; tablet filler; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Sucrose is widely used in oral pharmaceutical formulations.

Sucrose syrup, containing 50–67% w/w sucrose, is used in tableting as a binding agent for wet granulation. In the powdered form, sucrose serves as a dry binder (2–20% w/w) or as a bulking agent and sweetener in chewable tablets and lozenges.(1,2) Tablets that contain large amounts of sucrose may harden to give poor disintegration.

Sucrose syrups are used as tablet-coating agents at concentrations between 50% and 67% w/w. With higher concentrations, partial inversion of sucrose occurs, which makes sugar coating difficult.

Sucrose syrups are also widely used as vehicles in oral liquid-dosage forms to enhance palatability or to increase viscosity.(3,4)

Sucrose has been used as a diluent in freeze-dried protein products.(5,6)

Sucrose is also widely used in foods and confectionery, and therapeutically in sugar pastes that are used to promote wound healing.(7,8) *See* Table I.

Table I: Uses of sucrose.

Use	Concentration (% w/w)
Syrup for oral liquid formulations	67
Sweetening agent	67
Tablet binder (dry granulation)	2–20
Tablet binder (wet granulation)	50–67
Tablet coating (syrup)	50–67

8 Description

Sucrose is a sugar obtained from sugar cane (*Saccharum officinarum* Linné (Fam. Gramineae)), sugar beet (*Beta vulgaris* Linné (Fam. Chenopodiaceae)), and other sources. It contains no added substances. Sucrose occurs as colorless crystals, as crystalline masses or blocks, or as a white crystalline powder; it is odorless and has a sweet taste.

9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Density (bulk):
0.93 g/cm^3 (crystalline sucrose);
0.60 g/cm^3 (powdered sucrose).
Density (tapped):
1.03 g/cm^3 (crystalline sucrose);
0.82 g/cm^3 (powdered sucrose).
Density (true): 1.6 g/cm^3
Dissociation constant: pK_a = 12.62
Flowability: crystalline sucrose is free flowing, whereas powdered sucrose is a cohesive solid.
Melting point: 160–186°C (with decomposition)
Moisture content: finely divided sucrose is hygroscopic and absorbs up to 1% water.(9) *See* Figure 1.
Osmolarity: a 9.25% w/v aqueous solution is isoosmotic with serum.
Particle size distribution: powdered sucrose is a white, irregular-sized granular powder. The crystalline material consists of colorless crystalline, roughly cubic granules. *See* Figures 2 and 3.

Table II: Pharmacopeial specifications for sucrose.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Appearance of solution	+	+	—
Acidity or alkalinity	+	+	—
Specific optical rotation	+66.3° to +67.0°	+66.3° to +67.0°	⩾+65.9°
Color value	—	⩽45	—
Conductivity	+	+	—
Loss on drying	⩽0.1%	⩽0.1%	—
Bacterial endotoxins[(a)]	⩽0.25 IU/mg	⩽0.25 IU/mg	—
Dextrins[(a)]	+	+	—
Reducing sugars	—	+	—
Invert sugar	+	—	+
Chloride	—	—	⩽0.0035%
Sulfate	—	—	⩽0.006%
Sulfites	⩽15 ppm	⩽10 ppm	—
Calcium	—	—	⩽5 ppm
Heavy metals	—	—	⩽5 ppm
Lead	⩽0.5 ppm	⩽0.5 ppm	—
Residue on ignition	—	—	⩽0.05%
Organic volatile impurities	—	—	+

[(a)] If sucrose is to be used in large volume infusions.

Refractive index: n_D^{25} = 1.34783 (10% w/v aqueous solution)
Solubility: *see* Table III.
Specific gravity: *see* Table IV.

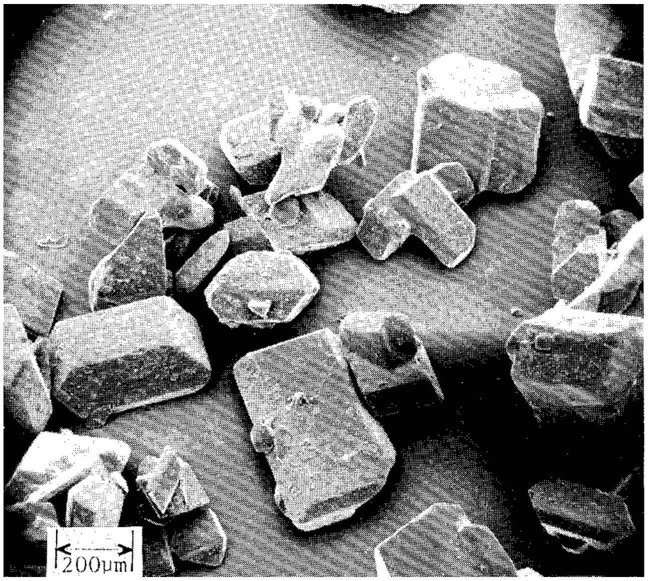
Table III: Solubility of sucrose.

Solvent	Solubility at 20°C unless otherwise stated
Chloroform	Practically insoluble
Ethanol	1 in 400
Ethanol (95%)	1 in 170
Propan-2-ol	1 in 400
Water	1 in 0.5
	1 in 0.2 at 100°C

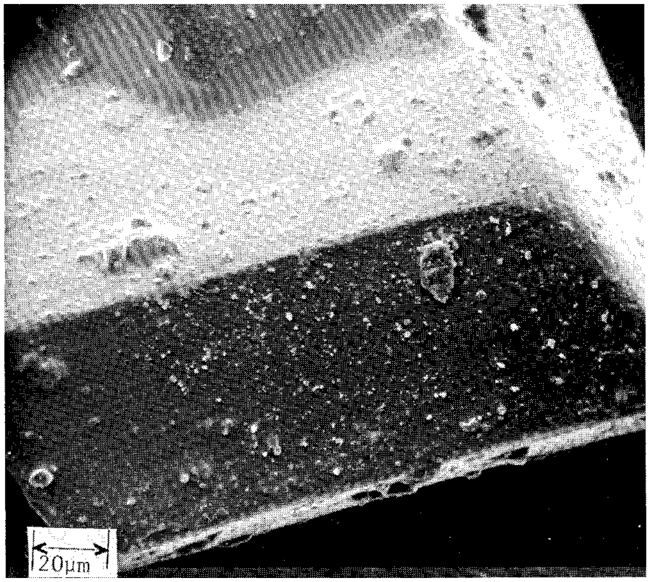
Table IV: Specific gravity of aqueous sucrose solutions.

Concentration of aqueous sucrose solution (% w/w)	Specific gravity at 20°C
2	1.0060
6	1.0219
10	1.0381
20	1.0810
30	1.1270
40	1.1764
50	1.2296
60	1.2865
70	1.3471
76	1.3854

SEM: 1
Excipient: Sucrose
Manufacturer: Great Western Sugar Co.
Lot No.: 1-2-80
Magnification: 60×
Voltage: 10 kV



SEM: 2
Excipient: Sucrose
Manufacturer: Great Western Sugar Co.
Lot No.: 1-2-80
Magnification: 600×
Voltage: 10 kV



11 Stability and Storage Conditions

Sucrose has good stability at room temperature and at moderate relative humidity. It absorbs up to 1% moisture, which is released upon heating at 90°C. Sucrose caramelizes when heated to temperatures above 160°C. Dilute sucrose solutions are liable to fermentation by microorganisms but resist decomposition at higher concentrations, e.g., above 60%

w/w concentration. Aqueous solutions may be sterilized by autoclaving or filtration.

When sucrose is used as a base for medicated confectionery, the cooking process, at temperatures rising from 110 to 145°C, causes some inversion to form dextrose and fructose (invert sugar). The fructose imparts stickiness to confectionery but prevents cloudiness due to graining. Inversion is accelerated particularly at temperatures above 130°C and by the presence of acids.

The bulk material should be stored in a well-closed container in a cool, dry place.

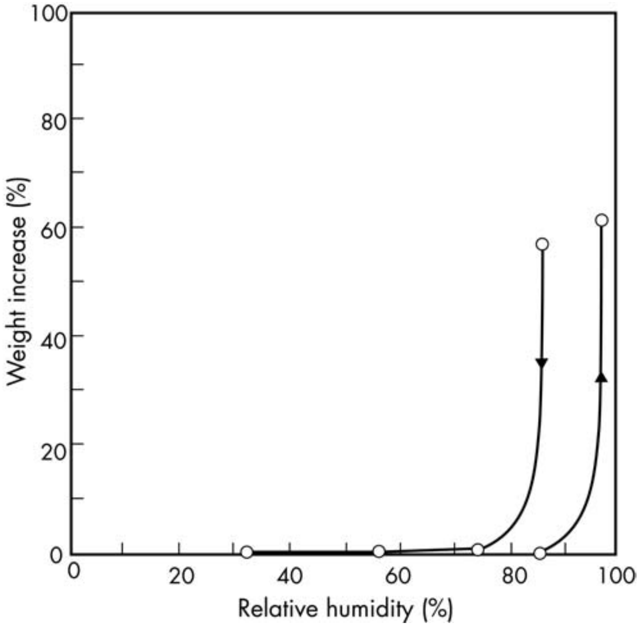


Figure 1: Moisture sorption–desorption isotherm of powdered sucrose.
Samples dried initially at 60°C over silica gel for 24 hours. Note: at 90% relative humidity, sufficient water was absorbed to cause dissolution of the solid.

12 Incompatibilities

Powdered sucrose may be contaminated with traces of heavy metals, which can lead to incompatibility with active ingredients, e.g. ascorbic acid. Sucrose may also be contaminated with sulfite from the refining process. With high sulfite content, color changes can occur in sugar-coated tablets; for certain colors used in sugar-coating the maximum limit for sulfite content, calculated as sulfur, is 1 ppm. In the presence of dilute or concentrated acids, sucrose is hydrolyzed or inverted to dextrose and fructose (invert sugar). Sucrose may attack aluminum closures.$^{(10)}$

13 Method of Manufacture

Sucrose is obtained from the sugar cane plant, which contains 15–20% sucrose, and sugar beet, which contains 10–17% sucrose. Juice from these sources is heated to coagulate water-soluble proteins, which are removed by skimming. The resultant solution is then decolorized with an ion-exchange resin or charcoal and concentrated. Upon cooling, sucrose crystallizes out. The remaining solution is concentrated again and yields more sucrose, brown sugar, and molasses.

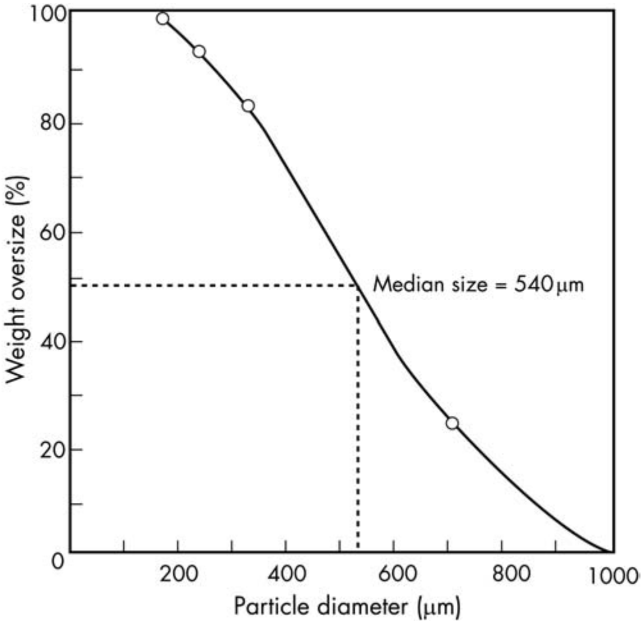


Figure 2: Particle size distribution of crystalline sucrose.

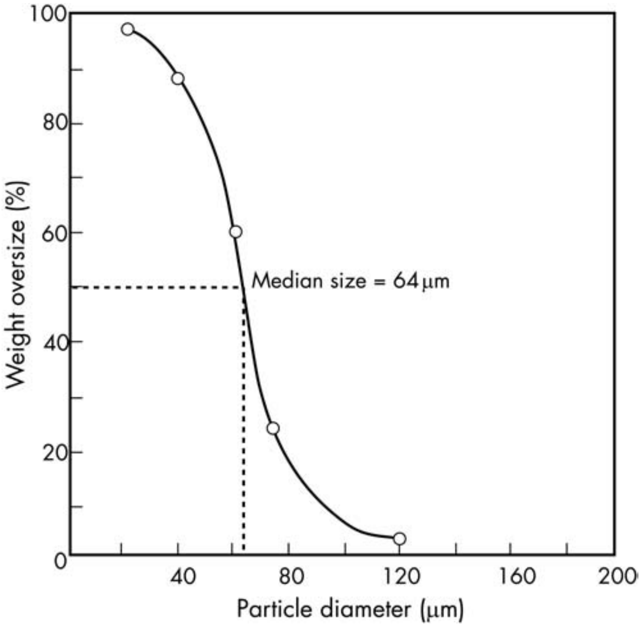


Figure 3: Particle size distribution of powdered sucrose.

14 Safety

Sucrose is hydrolyzed in the small intestine by the enzyme sucrase to yield dextrose and fructose, which are then absorbed. When administered intravenously, sucrose is excreted unchanged in the urine.

Although sucrose is very widely used in foods and pharmaceutical formulations, sucrose consumption is a cause of concern and should be monitored in patients with diabetes mellitus or other metabolic sugar intolerance.$^{(11)}$

Sucrose is also considered to be more cariogenic than other carbohydrates since it is more easily converted to dental plaque.

For this reason, its use in oral pharmaceutical formulations is declining.

Although sucrose has been associated with obesity, renal damage, and a number of other diseases, conclusive evidence linking sucrose intake with some diseases could not be established.(12,13) It was, however, recommended that sucrose intake in the diet should be reduced.(13)

LD_{50} (mouse, IP): 14 g/kg(14)
LD_{50} (rat, oral): 29.7 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. In the UK, the occupational exposure limit for sucrose is 10 mg/m^3 long-term (8-hour TWA) and 20 mg/m^3 short-term.(15)

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (injections; oral capsules, solutions, syrups, and tablets; topical preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Compressible sugar; confectioner's sugar; invert sugar; sugar spheres.

Invert sugar

Empirical formula: $C_6H_{12}O_6$
Molecular weight: 180.16
CAS number: [8013-17-0]
Comments: an equimolecular mixture of dextrose and fructose prepared by the hydrolysis of sucrose with a suitable mineral acid such as hydrochloric acid. Invert sugar may be used as a stabilizing agent to help prevent crystallization of sucrose syrups and graining in confectionery. A 10% aqueous solution is also used in parenteral nutrition.

18 Comments

For typical boiling points of sucrose syrups, without inversion of the sugar, *see* Table V. A specification for sucrose is contained in the Food Chemicals Codex (FCC).

The EINECS number for sucrose is 200-334-9.

Table V: Boiling points of sucrose syrups.

Sucrose concentration (% w/v)	Boiling point (°C)
50	101.5
60	103
64	104
72	105.5
75	107
77.5	108.5
80	110.5

19 Specific References

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3 Salazar DSM, Saavedra C. Application of a sensorial response model to the design of an oral liquid pharmaceutical dosage form. *Drug Dev Ind Pharm* 2000; **26**(1): 55–60.
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21 Authors

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22 Date of Revision

17 August 2005.

Sugar, Compressible

1 Nonproprietary Names

USPNF: Compressible sugar

2 Synonyms

Di-Pac; direct compacting sucrose.

3 Chemical name and CAS Registry Number

See Sections 4 and 18.

4 Empirical Formula and Molecular Weight

The USPNF 23 states that compressible sugar contains not less than 95.0% and not more than 98.0% of sucrose ($C_{12}H_{22}O_{11}$). It may contain starch, maltodextrin, or invert sugar, and may contain a suitable lubricant.

5 Structural Formula

See Section 4.

6 Functional Category

Sweetening agent; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Compressible sugar is used primarily in the preparation of direct-compression chewable tablets. Its tableting properties can be influenced by small changes in moisture level;(1,2) *see* Table I.

Table I: Uses of compressible sugar.

Use	Concentration (%)
Dry binder in tablet formulations	5–20
Filler in chewable tablets	20–60
Filler in tablets	20–60
Sweetener in chewable tablets	10–50

8 Description

Compressible sugar is a sweet-tasting, white, crystalline powder.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for compressible sugar.

Test	USPNF 23
Identification	+
Calcium	+
Chloride	$\leqslant$0.014%
Heavy metals	$\leqslant$5 ppm
Loss on drying	0.25–1.0%
Residue on ignition	$\leqslant$0.1%
Microbial limits	+
Organic volatile impurities	+
Sulfate	$\leqslant$0.010%
Assay	95.0–98.0%

10 Typical Properties

Density (bulk): 0.492 g/cm^3
Density (tapped): 0.6 g/cm^3
Moisture content: 0.57%
Particle size distribution: for *Di-Pac*, 3% maximum retained on a #40 (425 μm) mesh; 75% minimum through a #100 (150 μm) mesh; 5% maximum through #200 (75 μm) mesh.
Solubility: the sucrose portion is water-soluble.
Specific surface area: 0.13–0.14 m^2/g

11 Stability and Storage Conditions

Compressible sugar is stable in air under normal storage conditions of room temperature and low relative humidity. The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatible with dilute acids, which cause hydrolysis of sucrose to invert sugar, and with alkaline earth hydroxides, which react with sucrose to form sucrates.

13 Method of Manufacture

Compressible sugar is prepared by cocrystallization of sucrose with other excipients such as maltodextrin.(1) Compressible sugar may also be prepared using a dry granulation process.

14 Safety

Compressible sugar is generally regarded as a relatively nontoxic and nonirritant material. *See also* Sucrose.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. *See also* Sucrose.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Confectioner's sugar; sucrose; sugar spheres; *Sugartab*.

Sugartab

Appearance: *Sugartab* (JRS Pharma LC) is a compressible sugar that does not conform to the USPNF 23 specification. It is an agglomerated sugar product containing approximately 90–93% sucrose, the balance being invert sugar.
Density (bulk): 0.60 g/cm^3
Density (tapped): 0.69 g/cm^3
EINECS number: [64333-34-2]
Flowability: 42.7 g/s
Moisture content: 0.20–0.57%.
Particle size distribution: 30% through a #20 (850 μm) mesh; 3% through a #30 (600 μm) mesh.

18 Comments

—

19 Specific References

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2 Tabibi SE, Hollenbeck RG. Interaction of water vapor and compressible sugar. *Int J Pharm* 1984; **18**: 169–183.

20 General References

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Mendes RW, Gupta MR, Katz IA, O'Neil JA. Nu-tab as a chewable direct compression carrier. *Drug Cosmet Ind* 1974; **115**(6): 42–46, 130–133.
Ondari CO, Kean CE, Rhodes CT. Comparative evaluation of several direct compression sugars. *Drug Dev Ind Pharm* 1983; **9**: 1555–1572.
Ondari CO, Kean CE, Rhodes CT. Comparative evaluation of several direct compression sugars. *Drug Dev Ind Pharm* 1988; **14**: 1517–1527.
Shangraw RF, Wallace JW, Bowers FM. Morphology and functionality in tablet excipients for direct compression. *Pharm Technol* 1981; **5**: 69–78.

21 Authors

AW Wood.

22 Date of Revision

17 August 2005.

Sugar, Confectioner's

1 Nonproprietary Names

USPNF: Confectioner's sugar

2 Synonyms

Icing sugar; powdered sugar.

3 Chemical Name and CAS Registry Number

See Section 4.

4 Empirical Formula and Molecular Weight

The USPNF 23 describes confectioner's sugar as a mixture of sucrose ($C_{12}H_{22}O_{11}$) and corn starch that has been ground to a fine powder; it contains not less than 95.0% sucrose.

5 Structural Formula

See Section 4 and Sucrose.

6 Functional Category

Sugar coating adjunct; sweetening agent; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Confectioner's sugar is used in pharmaceutical formulations when a rapidly dissolving form of sugar is required for flavoring or sweetening. It is used as a diluent in solid-dosage formulations when a small particle size is necessary to achieve content uniformity in blends with finely divided active ingredients. In solutions, at high concentrations (70% w/v), confectioner's sugar provides increased viscosity along with some preservative effects. Confectioner's sugar is also used in the preparation of sugar-coating solutions and in wet granulations as a binder/diluent. *See* Table I.

Table I: Uses of confectioner's sugar.

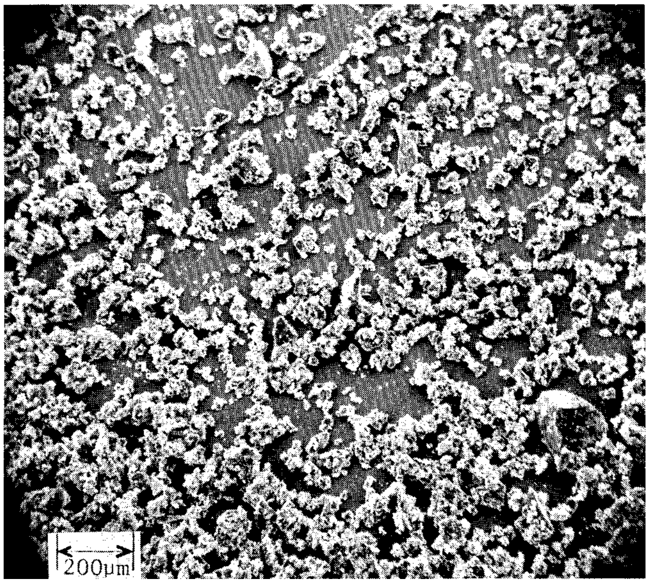
Use	Concentration (%)
Sweetening agent in tablets	10–20
Tablet diluent	10–50

See also Section 18.

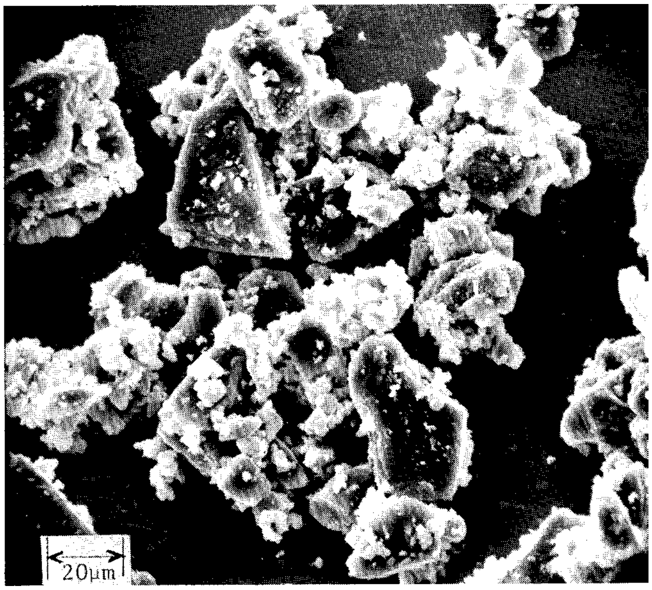
8 Description

Confectioner's sugar occurs as a sweet-tasting, fine, white, odorless powder.

SEM: 1
Excipient: Confectioner's sugar
Manufacturer: Frost
Lot No.: 101A-1
Magnification: 60×
Voltage: 20 kV



SEM: 2
Excipient: Confectioner's sugar
Manufacturer: Frost
Lot No.: 101A-1
Magnification: 600×
Voltage: 20 kV



9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for confectioner's sugar.

Test	USPNF 23
Identification	+
Chloride	⩽0.014%
Calcium	+
Heavy metals	⩽5 ppm
Loss on drying	⩽1.0%
Microbial limits	+
Organic volatile impurities	+
Residue on ignition	⩽0.08%
Specific rotation	⩾+62.6°
Sulfate	⩽0.006%
Assay	⩽95.0%

10 Typical Properties

Density (bulk): 0.465 g/cm^3
Density (tapped): 0.824 g/cm^3
Moisture content: 0.1–0.31%
Particle size distribution: various grades with different particle sizes are commercially available, e.g., 6X, 10X, and 12X grades of confectioner's sugar from the Domino Sugar Corp. Mean particle size is 14.3 μm.

For 6X, 94% through a #200 (75 μm) mesh.

For 10X, 99.9% through a #100 (150 μm) mesh and 97.5% through a #200 (75 μm) mesh.

For 12X, 99% through a #200 (75 μm) mesh and 96% through a #325 (45 μm) mesh.

Solubility: the sucrose portion is water-soluble while the starch portion is insoluble in water, although it forms a cloudy solution.

11 Stability and Storage Conditions

Confectioner's sugar is stable in air at moderate temperatures but may caramelize and decompose above 160°C. It is more hygroscopic than granular sucrose. Microbial growth may occur on dry storage if adsorbed moisture is present or in dilute aqueous solutions.

Confectioner's sugar should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Confectioner's sugar is incompatible with dilute acids, which cause the hydrolysis of sucrose to invert sugar. It is also incompatible with alkaline earth hydroxides, which react with sucrose to form sucrates.

13 Method of Manufacture

Confectioner's sugar is usually manufactured by grinding refined granulated sucrose with corn starch to produce a fine powder. Other anticaking agents, such as tricalcium phosphate and various silicates, have also been used but are less common.

14 Safety

Confectioner's sugar is used in confectionery and oral pharmaceutical formulations. It is generally regarded as a relatively nontoxic and nonirritant material. *See also* Sucrose.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. *See also* Sucrose.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (capsules and tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Compressible sugar; sucrose; sugar spheres.

18 Comments

Confectioner's sugar is not widely used in pharmaceutical formulations because the poor-flow characteristics prevent its use in direct-compression blends. However, confectioner's sugar is used when a smooth mouth feel or a rapidly dissolving sweetener is required, and when a milled/micronized active ingredient must be blended with a diluent of similar particle size for powders or wet granulations.

Low-starch grades of confectioner's sugar containing 0.01% w/w starch are also commercially available.

19 Specific References

20 General References

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21 Authors

AH Kibbe.

22 Date of Revision

12 August 2005.

Sugar Spheres

1 Nonproprietary Names

BP: Sugar spheres
PhEur: Sacchari spheri
USPNF: Sugar spheres

2 Synonyms

Non-pareil; non-pareil seeds; *NPTAB*; *Nu-Core*; *Nu-Pareil PG*; sugar seeds; *Suglets*.

3 Chemical Name and CAS Registry Number

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4 Empirical Formula and Molecular Weight

See Section 8.

5 Structural Formula

See Section 8.

6 Functional Category

Tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Sugar spheres are mainly used as inert cores in capsule and tablet formulations, particularly multiparticulate sustained-release formulations.(1–4) They form the base upon which a drug is coated, usually followed by a release-modifying polymer coating.

Alternatively, a drug and matrix polymer may be coated onto the cores simultaneously. The active drug is released over an extended period either via diffusion through the polymer or through to the controlled erosion of the polymer coating.

Complex drug mixtures contained within a single-dosage form may be prepared by coating the drugs onto different batches of sugar spheres with different protective polymer coatings.

Sugar spheres are also used in confectionery products.

8 Description

The USPNF 23 describes sugar spheres as approximately spherical granules of a labeled nominal-size range with a uniform diameter and containing not less than 62.5% and not more than 91.5% of sucrose, calculated on the dried basis. The remainder is chiefly starch.

The PhEur 2005 states that sugar spheres contain not more than 92% of sucrose calculated on the dried basis. The remainder consists of corn (maize) starch and may also contain starch hydrolysates and color additives. The diameter of sugar spheres varies from 200 to 2000 μm and the upper and lower limits of the size of the sugar spheres are stated on the label.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sugar spheres.

Test	PhEur 2005	USPNF 23
Identification	+	+
Heavy metals	⩽5 ppm	⩽5 ppm
Loss on drying	⩽5.0%	⩽4.0%
Microbial limits	+	+
Organic volatile impurities	—	+
Particle size distribution	+	+
Residue on ignition	⩽0.2%	⩽0.25%
Specific rotation	—	+41° to +61°
Sucrose (dried basis)	⩽92%	62.5–91.5%

10 Typical properties

Density:
1.57–1.59 g/cm^3 for *Suglets* less than 500 μm in size;
1.55–1.58 g/cm^3 for *Suglets* more than 500 μm in size.

Flowability: <10 seconds, free flowing.

Particle size distribution: sugar spheres are of a uniform diameter. The following sizes are commercially available from various suppliers (US standard sieves):
45–60 mesh (250–355 μm)
40–50 mesh (300–425 μm)
35–45 mesh (355–500 μm)
35–40 mesh (420–500 μm)
30–35 mesh (500–600 μm)
25–30 mesh (610–710 μm)
20–25 mesh (710–850 μm)
18–20 mesh (850–1000 μm)
16–20 mesh (850–1180 μm)
14–18 mesh (1000–1400 μm)

Solubility: solubility in water varies according to the sucrose-to-starch ratio. The sucrose component is freely soluble in water, whereas the starch component is practically insoluble in cold water.

Specific surface area:
0.1–0.2 m^2/g for *Suglets* less than 500 μm in size;
>0.2 m^2/g for *Suglets* more than 500 μm in size.

11 Stability and Storage Conditions

Sugar spheres are stable when stored in a well-closed container in a cool, dry place.

12 Incompatibilities

See Starch and Sucrose for information concerning the incompatibilities of the component materials of sugar spheres.

13 Method of Manufacture

Sugar spheres are prepared from crystalline sucrose, which is coated using sugar syrup and a starch dusting powder.

14 Safety

Sugar spheres are used in oral pharmaceutical formulations. The sucrose and starch components of sugar spheres are widely used in edible food products and oral pharmaceutical formulations.

The adverse reactions and precautions necessary with the starch and sucrose components should be considered in any product containing sugar spheres. For example, sucrose is generally regarded as more cariogenic than other carbohydrates, and in higher doses is also contraindicated in diabetic patients.

See Starch and Sucrose for further information.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK and Europe. The sucrose and starch components of sugar spheres are individually approved for use as food additives in Europe and the USA. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Compressible sugar; confectioner's sugar; starch; sucrose.

18 Comments

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19 Specific References

1 Narsimhan R, Labhasetwar VD, Lakhotia CL, Dorle A. Timed-release noscapine microcapsules. *Indian J Pharm Sci* 1988; **50**: 120–122.

2 Bansal AK, Kakkar AP. Solvent deposition of diazepam over sucrose pellets. *Indian J Pharm Sci* 1990; **52**: 186–187.

3 Ho H-O, Su H-L, Tsai T, Sheu M-T. The preparation and characterization of solid dispersions on pellets using a fluidized-bed system. *Int J Pharm* 1996; **139**: 223–229.

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20 General References

Birch GG, Parker KJ, eds. *Sugar: Science and Technology.* London: Applied Science Publications, 1979.

21 Authors

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22 Date of Revision

26 August 2005.

Sulfobutylether β-Cyclodextrin

1 Nonproprietary Names

None adopted.

2 Synonyms

β-Cyclodextrin sulfobutylether, sodium salt; *Captisol*; (SBE)$_{7m}$-beta-CD; SBE7-β-CD; SBECD; sulfobutylether-β-cyclodextrin, sodium salt.

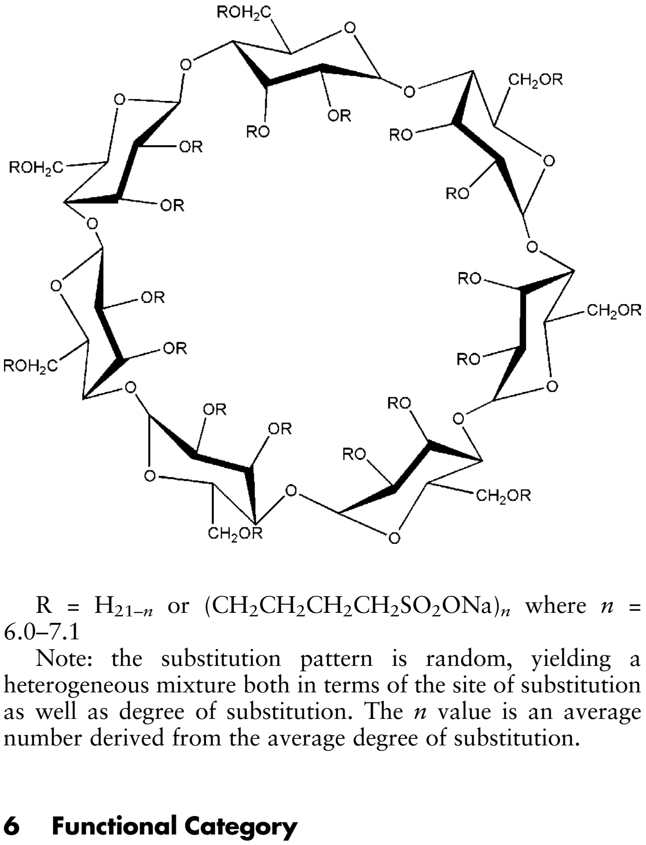
3 Chemical Name and CAS Registry Number

β-Cyclodextrin sulfobutylether, sodium salt [1824100-00-0]

4 Empirical Formula and Molecular Weight

$C_{42}H_{70-n}O_{35}\cdot(C_4H_8SO_3Na)_n$ 2163 (where n = approximately 6.5)

5 Structural Formula



R = H_{21-n} or $(CH_2CH_2CH_2CH_2SO_2ONa)_n$ where n = 6.0–7.1

Note: the substitution pattern is random, yielding a heterogeneous mixture both in terms of the site of substitution as well as degree of substitution. The n value is an average number derived from the average degree of substitution.

6 Functional Category

Dissolution-enhancing agent; drug delivery system; osmotic agent; solubilizing agent; stabilizing agent; tablet and capsule diluent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Cyclodextrins are crystalline, nonhygroscopic, cyclic oligosaccharides derived from starch (*see* Cyclodextrins). Sulfobutylether β-cyclodextrin is an amorphous, anionic substituted β-cyclodextrin derivative (*see* Section 8); other substituted cyclodextrin derivatives are also available (*see* Section 17).

Sulfobutylether β-cyclodextrin can form noncovalent complexes with many types of compounds including small organic molecules, peptides,(1) and proteins.(2) It can also enhance their solubility(3,4) and stability(4–6) in water. The first application of sulfobutylether β-cyclodextrin was in injectable preparations;(7) it can also be used in oral solid(8,9) and liquid(10) dosage forms, and ophthalmic,(11,12) inhalation, and intranasal formulations.(13) Sulfobutylether β-cyclodextrin can function as an osmotic agent and/or a solubilizer for controlled-release delivery,(9) and has antimicrobial preservative properties when present at sufficient concentrations.

The amount of sulfobutylether β-cyclodextrin that may be used is dependent on the purpose for inclusion in the formulation, the route of administration, and the ability of the cyclodextrin to complex with the drug being delivered. The minimum amount required for solubilization is, in general, a cyclodextrin/drug molar ratio of approximately 1–5 (the exact ratio being experimentally determined from complexation data). The maximum use in a formulation may be limited by physicochemical constraints such as viscosity (e.g. syringeable concentrations may be considered up to 50% w/v), tonicity, or the total weight and size of solid dosage forms (e.g. less than a gram in an individual tablet). It may also be limited by pharmacokinetic/pharmacodynamic (PK/PD) considerations. As dilution of a cyclodextrin formulation leads to an increase in the amount of uncomplexed drug, formulations that are not diluted upon administration, such as ophthalmic formulations, are sensitive to cyclodextrin concentration. In formulations such as these, cyclodextrin concentrations greater than the minimum required for solubilization can reduce the availability of uncomplexed drug and thereby affect PK/PD expectations by producing effects such as slower onset, lower C_{max}, and bioavailability.

8 Description

β-Cyclodextrin is a cyclic oligosaccharide containing seven D-(+)-glucopyranose units attached by α(1→4) glucoside bonds (*see* Cyclodextrins). Sulfobutylether β-cyclodextrin is an anionic β-cyclodextrin derivative with a sodium sulfonate salt separated from the hydrophobic cavity by a butyl spacer group. The substituent is introduced at positions 2, 3, and 6 in at least one of the glucopyranose units in the cyclodextrin structure. Introducing the SBE into β-cyclodextrin can produce materials with different degrees of substitution, theoretically from 1 to 21; the hepta-substituted preparation (SBE7-β-CD) being the cyclodextrin with the most desirable drug carrier properties.(14)

Sulfobutylether β-cyclodextrin occurs as a white amorphous powder.

9 Pharmacopeial Specifications

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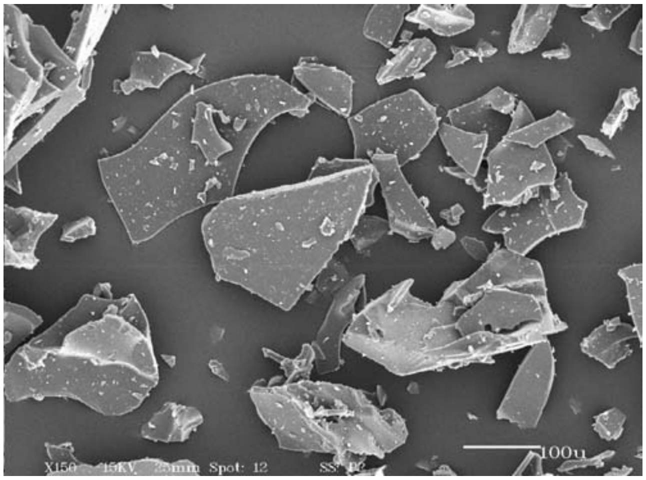
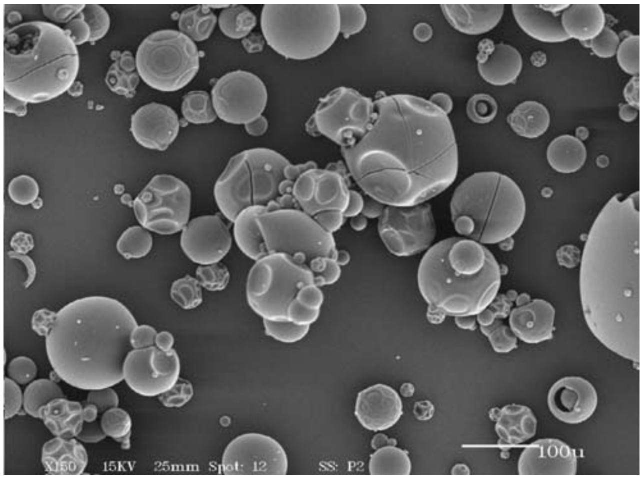
10 Typical Properties

Acidity/alkalinity: pH = 6 (30% w/w aqueous solution)$^{(15)}$
Angle of repose:
20.5° for freeze-dried *Captisol*;
31.6° for spray-dried *Captisol*.
Appearance of solution: a 30% w/v solution in water is clear, colorless, and essentially free from particles of foreign matter.
Average degree of substitution: 6.0–7.1$^{(15)}$
Compressibility: *see* Figure 1.
Density (bulk):
0.446–0.482 g/cm^3 for freeze-dried *Captisol*;
0.524 g/cm^3 for spray-dried *Captisol*;
0.482 g/cm^3 for spray-agglomerated reprocessed *Captisol*.
Density (tapped):
0.565–0.597 g/cm^3 for freeze-dried *Captisol*;
0.624 g/cm^3 for spray-dried *Captisol*;
0.595 g/cm^3 for spray-agglomerated reprocessed *Captisol*.
Flowability: 50 g/s for freeze-dried *Captisol*.
Hygroscopicity: reversibly picks up water at relative humidities (RH) up to 60%. Equilibration at RH equal to or above 60% will result in deliquescence and a water content of approximately 16%w/w. *See* Figure 2.
Melting point: decomposition at 275°C.
Moisture content: 2–5% typically; maximum 10%.
Osmolarity: a 12.7% w/v solution of *Captisol* is iso-osmotic with serum.
Particle size distribution: typical mean particle size for spray-dried sulfobutylether β-cyclodextrin sodium is 70–120 μm. Various processing and handling methods may result in different nominal mean particle sizes.
Specific rotation $[\alpha]_D^{20}$**:** +94°
Solubility: soluble 1 in less than 2 of water; 1 in 30–40 of methanol; practically insoluble in ethanol, *n*-hexane, 1-butanol, acetonitrile, 2-propanol, and ethyl acetate.
Viscosity (dynamic): 1.75 mPa s for a 8.5% w/w aqueous solution at 25°C, 1.09 mPa s at 60°C;
528 mPa s for a 60% w/w aqueous solution at 25°C, 87 mPa s at 60°C.$^{(15)}$

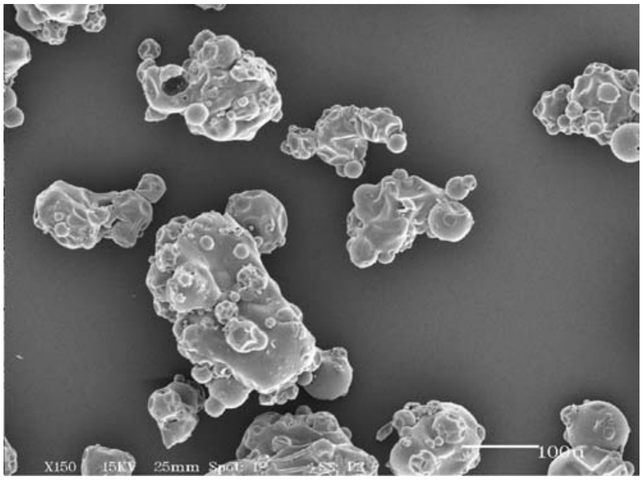
SEM: 1
Excipient: Freeze-dried sulfobutylether β-cyclodextrin sodium (*Captisol*)
Manufacturer: CyDex
Magnification: 150×



SEM: 2
Excipient: Spray-dried sulfobutylether β-cyclodextrin sodium (*Captisol*)
Manufacturer: CyDex
Magnification: 150×



SEM: 3
Excipient: Spray-agglomerated sulfobutylether β-cyclodextrin sodium (reprocessed *Captisol*)
Manufacturer: CyDex
Magnification: 150×



11 Stability and Storage Conditions

Sulfobutylether β-cyclodextrin is stable in the solid state and should be protected from high humidity. It should be stored in a tightly sealed container in a cool, dry place.

It will reversibly take up moisture without any effect on the appearance of the material at humidities up to 60% RH. Equilibration at RH values above 60% will result in deliquescence. Once in this state, the material can be dried, but will give a glasslike product. This water absorption behavior is typical of amorphous hygroscopic materials.

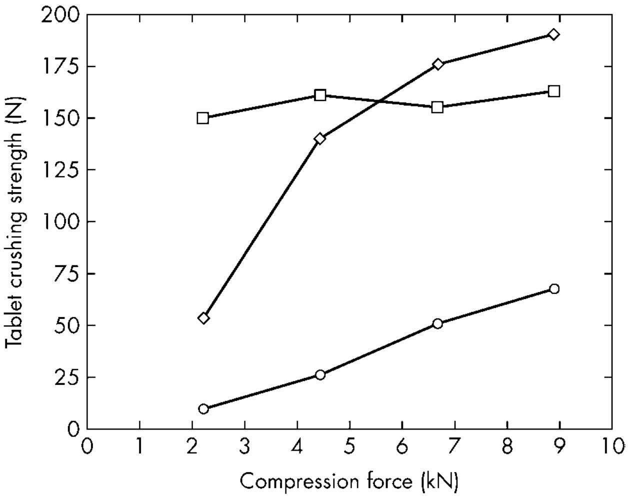


Figure 1: Compression characteristics of sulfobutylether β-cyclodextrin sodium.
○: Spray-dried (CyDex, *Captisol*, Lot No.: CY-03A-02046)
◇: Spray-agglomerated (Reprocessed CyDex Lot No.: CY-03A-099020)
□: Freeze-dried (CyDex, *Captisol*, Lot No.: RPP-96-CDSBE-BA#1)
Mean tablet weight: 220 mg
Tablet dimensions: 5/16 inch std concave
Lubricated with 0.5% magnesium stearate
Tablet machine: Instrumented Stokes Model F, Single Punch Press

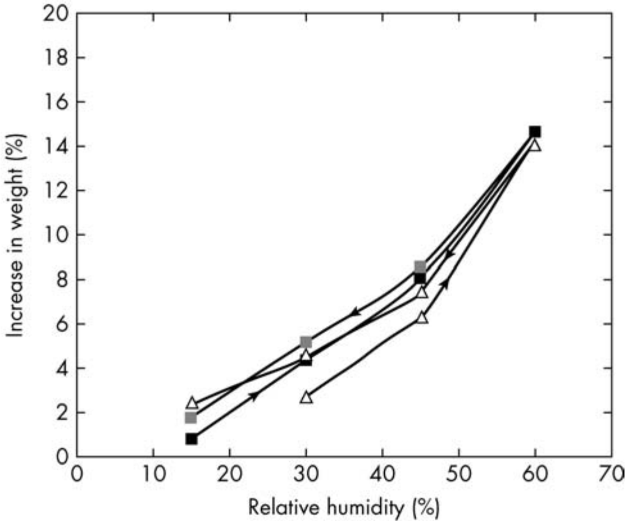


Figure 2: Moisture sorption–desorption isotherm of sulfobutylether β-cyclodextrin sodium, at 30°C.
■: Freeze-dried (native moisture content: 3.7%)
△: Spray-dried (native moisture content: 5.2%)

Sulfobutylether β-cyclodextrin is stable in aqueous solutions at values above about pH1. It can degrade in highly acidic (pH < 1) solutions, particularly at elevated temperatures; producing the ring-opened form, followed by hydrolysis of the α(1→4) glucoside bonds.

Sulfobutylether β-cyclodextrin solutions may be autoclaved.(15)

12 Incompatibilities

The preservative activity of benzalkonium chloride is reduced in the presence of sulfobutylether β-cyclodextrin.

13 Method of Manufacture

Sulfobutylether β-cyclodextrin is prepared by alkylation of β-cyclodextrin using 1,4-butane sultone under basic conditions. The degree of substitution in β-cyclodextrin is controlled by the stoichiometric ratio of β-cyclodextrin to sultone used in the process.

14 Safety

Sulfobutylether β-cyclodextrin is derived from β-cyclodextrin, which is toxic when administered parenterally (*see* Cyclodextrins). However, studies have shown that sulfobutylether β-cyclodextrin is well tolerated at high doses, when administered via intravenous bolus injections, orally, and by inhalation.(1,8,16) Up to 9 g/day may be administered by IV infusion in a licensed voriconazole formulation.(15)

Sulfobutylether β-cyclodextrin has been subjected to an extensive battery of *in vitro* and *in vivo* genotoxicity and pharmacological evaluations. No genotoxic or mutagenic changes were observed with sulfobutylether β-cyclodextrin administration. Sulfobutylether β-cyclodextrin is biocompatible and exhibits no pharmacological activity. It is rapidly eliminated unmetabolized when administered intravenously.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Sulfobutylether β-cyclodextrin is included in IV and IM injectable products currently approved and marketed in the USA and Europe. It is included in the FDA inactive ingredient guide for IM and IV use. Its use by other routes, including oral, inhalation, and ophthalmic, is being evaluated in clinical studies.

17 Related Substances

α-Cyclodextrin; β-cyclodextrin; γ-cyclodextrin; dimethyl-β-cyclodextrin; 2-hydroxyethyl-β-cyclodextrin; 2-hydroxypropyl-β-cyclodextrin; 3-hydroxypropyl-β-cyclodextrin; trimethyl-β-cyclodextrin.

18 Comments

In addition to its use in pharmaceutical formulations, sulfobutylether β-cyclodextrin is also used in chromatographic separations, particularly in chiral separations by HPLC(17) and capillary electrophoresis(18–21) and in tissue imaging.(22)

19 Specific References

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11 Jarho P, Jarvinen K, Urtti A, Stella V, Jarvinen T. The use of cyclodextrins in ophthalmic formulations of dipivefrin. *Int J Pharm* 1997; **153**: 225–233.
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GL Mosher, JD Pipkin.

22 Date of Revision

1 September 2005.

Sulfuric Acid

1 Nonproprietary Names

BP: Sulphuric acid
PhEur: Acidum sulfuricum
USPNF: Sulfuric acid

2 Synonyms

E513; hydrogen sulfate; oil of vitriol.

3 Chemical Name and CAS Registry Number

Sulfuric acid [7664-93-9].

4 Empirical Formula and Molecular Weight

H_2SO_4 98.08

5 Structural Formula

H_2SO_4

6 Functional Category

Acidifying agent.

7 Applications in Pharmaceutical Formulation or Technology

Sulfuric acid is used as an acidifying agent in a variety of pharmaceutical and food preparations. It may also be used to prepare dilute sulfuric acid, which, in addition to its use as an excipient, has some therapeutic use for the treatment of gastric hypoacidity, as an astringent in diarrhea, or to stimulate appetite. Sulfuric acid has been used in parenteral, oral, topical, and ophthalmic pharmaceutical formulations.

8 Description

Sulfuric acid occurs as a clear, colorless, odorless, oily liquid. It is very corrosive and has a great affinity for water.

The USPNF 23 specifies that sulfuric acid contains not less than 95% and not more than 98%, by weight, of H_2SO_4; the remainder is water. *See also* Section 9.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sulfuric acid.

Test	PhEur 2005	USPNF 23
Identification	+	+
Appearance of solution	+	—
Residue on ignition	—	⩽0.005%
Chloride	⩽50 ppm	⩽0.005%
Arsenic	⩽1 ppm	⩽1 ppm
Heavy metals	⩽5 ppm	⩽5 ppm
Weight per mL	≈1.84	—
Iron	⩽25 ppm	—
Nitrate	+	—
Reducing substances	—	+
Assay (of H_2SO_4)	95.0–100.5%	95.0–98.0%

10 Typical Properties

Boiling point:
≈290°C for H_2SO_4 (95%–98% w/w);
330°C for H_2SO_4 (100% w/w).
Density: ≈1.84 g/cm^3 at 20°C
Dissociation constant:
$pK_{a1} = -3.00$;
$pK_{a2} = 1.99$.
Freezing point:
10°C for H_2SO_4 (100% w/w);
3°C for H_2SO_4 (98% w/w);
−32°C for H_2SO_4 (93% w/w).
Solubility: miscible with ethanol and water.
Vapor density: 3.4 (air = 1.0)
Vapor pressure: <0.3 mmHg at 20°C

11 Stability and Storage Conditions

Sulfuric acid is stable but very corrosive and hygroscopic. It will draw moisture from the atmosphere. Sulfuric acid should be stored in a tightly closed container in an explosion-proof area. Containers should be stored out of direct sunlight and away from heat. Avoid heat and moisture. Isolate from incompatible materials. *See also* Section 12.

12 Incompatibilities

Avoid storage in close proximity to water, most common metals, organic materials, strong reducing agents, combustible materials, strong bases, carbonates, sulfides, cyanides, strong oxidizing agents, and carbides.

Sulfuric acid is a powerful oxidizer and may ignite or explode on contact with many materials.

It can react violently with the evolution of a large amount of heat. Oxides of sulfur and hydrogen can be generated during reactions.

Great care must be exercised when mixing with other liquids.

13 Method of Manufacture

Sulfuric acid may be prepared industrially by either the contact process or the chamber process.(1,2)

Contact Process

$2SO_2 + O_2 \rightarrow 2SO_3$

$SO_3 + H_2O \rightarrow H_2SO_4$

Chamber Process

$2NO + O_2 \rightarrow 2NO_2$

$NO_2 + SO_2 + H_2O \rightarrow H_2SO_4 + NO$

14 Safety

Sulfuric acid is widely used in a variety of pharmaceutical formulations. Although concentrated sulfuric acid is very corrosive, it is normally used well diluted in formulations. Concentrated sulfuric acid will react violently with water and much heat is generated. When diluting sulfuric acid, the acid should always be added to the other liquid with great caution.

The concentrated solution is extremely corrosive and can cause severe damage or necrosis on contact with the eyes and skin. Ingestion may cause severe injury or death. Inhalation of concentrated vapors can cause serious lung damage.

LD_{50} (rat, oral): 2.14 g/kg(3)

15 Handling Precautions

Caution should be exercised when handling sulfuric acid and suitable protection against inhalation and spillage should be made. Respiratory protection may not be required where adequate ventilation exists. Eye protection (safety goggles and face shield), rubber gloves, and apron are recommended, depending on the circumstances and quantity of sulfuric acid handled. Do not dilute spills of concentrated acid with water since an exothermic reaction will occur. Spills should be neutralized with soda ash or lime. Splashes on the skin and eyes should be treated by immediate and prolonged washing with large amounts of water followed by the application of sodium bicarbonate and medical attention should be sought.

Fumes can cause irritation or permanent damage to the eyes, nose, and respiratory system; prolonged exposure to fumes may damage the lungs.

In the UK, the long-term exposure limit (8-hour TWA) for sulfuric acid is 1 mg/m^3.(4,5)

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IM, IV, and IP injections, inhalation solutions, irrigation solutions, nasal, ophthalmic solutions and suspensions, oral solutions, and topical emulsions and creams). Included in nonparenteral and parenteral medicines licensed in Europe. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Dilute sulfuric acid; fuming sulfuric acid.

Dilute sulfuric acid

Density: 1.062–1.072 g/cm^3

Comments: prepared by adding 104 g of sulfuric acid to 896 g of purified water with constant stirring and cooling. Dilute sulfuric acid contains between 9.5% and 10.5% w/w of H_2SO_4.

Fuming sulfuric acid

Synonyms: oleum.

Comments: fuming sulfuric acid consists of H_2SO_4 with free sulfur trioxide (SO_3). It is prepared by adding sulfur trioxide to sulfuric acid. Available in grades containing up to about 80% free SO_3.

Fuming sulfuric acid is a colorless or slightly colored, viscous liquid that emits choking fumes of sulfur trioxide. It is extremely corrosive and should be handled with great care and stored in tightly closed glass-stoppered bottles.

18 Comments

A specification for sulfuric acid is contained in the Food Chemicals Codex (FCC). The EINECS number for sulfuric acid is 231-639-5.

19 Specific References

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20 General References

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21 Authors

GE Amidon.

22 Date of Revision

17 August 2005.

Sunflower Oil

1 Nonproprietary Names

BP: Sunflower oil, refined
PhEur: Helianthi annui oleum raffinatum

2 Synonyms

Huile de tournesol; oleum helianthi; sunflowerseed oil.

3 Chemical Name and CAS Registry Number

Sunflower oil [8001-21-6]

4 Empirical Formula and Molecular Weight

See Section 5.

5 Structural Formula

Sunflower oil is classified as an oleic–linoleic acid oil. Its composition includes linoleic acid (66%), oleic acid (21.3%), palmitic acid (6.4%), arachidic acid (4.0%), stearic acid (1.3%), and behenic acid (0.8%).

The PhEur 2005 describes sunflower oil as the refined fatty oil obtained from the seeds of *Helianthus annus* C. by mechanical expression or by extraction. A suitable antioxidant may be added.

6 Functional Category

Diluent; emollient; emulsifying agent; solvent; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Sunflower oil is widely used as an edible oil, primarily in oleomargarine. It is also used extensively in cosmetics and pharmaceutical formulations.

Therapeutically, sunflower oil is used to provide energy and essential fatty acids for parenteral nutrition. Studies have shown that sunflower oil may be used in intramuscular injections without inducing tissue damage.(1)

8 Description

Sunflower oil occurs as a clear, light yellow-colored liquid with a bland, agreeable taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sunflower oil.

Test	PhEur 2005
Identification	+
Characters	+
Acid value	⩽0.5
Peroxide value	⩽10.0
Unsaponifiable matter	⩽1.5%
Alkaline impurities	+
Composition of fatty acids	+
Palmitic acid	4.0–9.0%
Stearic acid	1.0–7.0%
Oleic acid	14.0–40.0%
Linoleic acid	48.0–74.0%

10 Typical Properties

Boiling point: 40–60°C
Density: 0.915–0.919
Hydroxyl value: 14–16
Iodine number: 125–140
Melting point: −18°C
Refractive index:
n_D^{25} = 1.472–1.474;
n_D^{40} = 1.466–1.468.
Saponification number: 188–194
Solubility: miscible with benzene, chloroform, carbon tetrachloride, diethyl ether, and light petroleum; practically insoluble in ethanol (95%) and water.

11 Stability and Storage Conditions

Sunflower oil should be stored in an airtight, well-filled container, protected from light. Stability may be improved by the addition of an antioxidant such as butylated hydroxytoluene.

12 Incompatibilities

The oxidative stability of sunflower oil is reduced in the presence of iron oxides and zinc oxide.(2)

Sunflower oil forms a 'skin' after being exposed to air for 2–3 weeks.

13 Method of Manufacture

Sunflower oil is obtained from the fruits and seeds (achenes) of the sunflower, *Helianthus annus* (Compositae), by mechanical means or by extraction.

14 Safety

Sunflower oil is widely used in food products and on its own as an edible oil. It is also used extensively in cosmetics and topical pharmaceutical formulations and is generally regarded as a relatively nontoxic and nonirritant material.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. When heated to decomposition, sunflower oil emits acrid smoke and irritating fumes.

16 Regulatory Status

GRAS listed. Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Corn oil; cottonseed oil; peanut oil; sesame oil; soybean oil.

18 Comments

High oleic acid content sunflower oil with good oxidative stability and emollient properties is commercially available for use in cosmetic formulations.(3) Sunflower oil with marked oxidative stability is particularly suitable for the manufacture of sunscreen agents.(4)

Sunflower oil should be labeled to indicate the name and concentration of any antioxidant added, and also whether the oil was obtained by mechanical expression or extraction. A specification for sunflower oil is contained in the Food Chemicals Codex (FCC).

The EINECS number for sunflower oil is 232-273-9.

19 Specific References

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4 Arquette DJ, Brown J, Dwyer K, Reinhardt J. Oils and fats: place in the sun. *Soap Perfum Cosmet* 1994; **67**(Nov): 49, 51.

20 General References

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21 Authors

SC Owen, PJ Sheskey.

22 Date of Revision

12 August 2005.

Suppository Bases, Hard Fat

1 Nonproprietary Names

BP: Hard fat
PhEur: Adeps solidus
USPNF: Hard fat

2 Synonyms

Adeps neutralis; *Akosoft*; *Akosol*; *Cremao CS-34*; *Cremao CS-36*; hydrogenated vegetable glycerides; *Massa estarinum*; *Massupol*; *Novata*; semisynthetic glycerides; *Suppocire*; *Wecobee*; *Witepsol*.

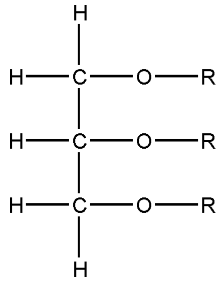
3 Chemical Name and CAS Registry Number

Hard fat triglyceride esters

4 Empirical Formula and Molecular Weight

Hard fat suppository bases consist mainly of mixtures of the triglyceride esters of the higher saturated fatty acids ($C_8H_{17}COOH$ to $C_{18}H_{37}COOH$) along with varying proportions of mono- and diglycerides. Special grades may contain additives such as beeswax, lecithin, polysorbates, ethoxylated fatty alcohols, and ethoxylated partial fatty glycerides.

5 Structural Formula



where R = H or $OC(CH_2)_nCH_3$; $n = 7–17$
Not all Rs can be H at the same time.

6 Functional Category

Suppository base.

7 Applications in Pharmaceutical Formulation or Technology

The primary application of hard fat suppository bases, or semisynthetic glycerides, is as a vehicle for the rectal or vaginal administration of a variety of drugs, either to exert local effects or to achieve systemic absorption.

Selection of a suppository base cannot usually be made in the absence of knowledge of the physicochemical properties and intrinsic thermodynamic activity of the drug substance. Other drug-related factors that can affect release and absorption and which must therefore be considered are the particle size distribution of insoluble solids, the oil : water partition coefficient, and the dissociation constant. The displacement value should also be known, as well as the ratio of drug to base. Properties of the suppository base that may or may not be modified by the drug, or that can influence drug release, are the melting characteristics, chemical reactivity, and rheology. The presence of additives in the base can also affect performance.

Melting characteristics Fatty-based suppositories intended for systemic use should liquefy at just below body temperature. Softening or dispersion may be adequate for suppositories intended for local action or modified release. High-melting-point bases may be indicated for fat-soluble drugs that tend to depress the melting point of bases or for suppositories used in warm climates. Drugs that dissolve in bases when hot may create problems if they deposit as crystals of different form or increased size on cooling or on storage. Low-melting-point bases, particularly those that melt to liquids of low viscosity, can be of value when large volumes of insoluble substances are to be incorporated; there is a risk of sedimentation in such instances. An important factor during processing is the time required for setting. This is affected by the temperature difference between the melting point and the solidification point.(1,2)

Chemical reactivity Although the use of bases with low hydroxyl values (low partial ester content) is indicated to minimize the risk of interaction with chemically reactive compounds, formulators should be aware that hydroxyl values are also related to hydrophilic properties, which, in turn, can modify both release and absorption rates. Bases with low hydroxyl values tend to be less plastic than those with higher values and, if cooled rapidly, may become excessively brittle. Peroxide values give a measure of the resistance of the base to oxidation and are a guide to the onset of rancidity.

Rheology The viscosity of the melted base can affect the uniformity of distribution of suspended solids during manufacture. It can also influence the release and absorption of the drug in the rectum. Further reduction in the particle size of insoluble solids is the method of choice to minimize the risk of sedimentation. However, the presence of a high content of fine, suspended particles is likely to increase viscosity. It may also make pouring difficult, delay melting, and induce brittleness on solidification. Additives are sometimes included to modify rheological properties and to maintain homogeneity, e.g. microcrystalline wax, but the extent of their effect on drug release should first be assessed. Release from a base in which viscosity has been enhanced by an added thickener may vary and be related to the aqueous solubility of the drug itself.

Additives Some grades of commercial bases already contain additives, and these are usually identified by the manufacturers by means of suitable letters and numbers. Additives may also be incorporated by formulators. Properties of suppositories that have been modified and additives or types of additives that have been used are shown in Table I. Water is undesirable as an additive because it enhances hydrolysis and the potential for a chemical reaction between constituents of the suppository. In low concentration, water plays little part in drug release and can serve as a medium for microbial growth.

Table I: Selected suppository additives.

Property	Additive
Dispersants (release and/or absorption enhancers)	Surfactants
Hygroscopicity (reduced)	Colloidal silicon dioxide
Hardeners (or increasing melting point)	Beeswax Cetyl alcohol Stearic acid Stearyl alcohol Aluminum monostearate (or di- and tristearate) Bentonite Magnesium stearate Colloidal silicon dioxide
Plasticizers (or decreasing melting point)	Glyceryl monostearate Myristyl alcohol Polysorbate 80 Propylene glycol

8 Description

A white or almost white, practically odorless, waxy, brittle mass. When heated to 50°C it melts to give a colorless or slightly yellowish liquid.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for suppository bases.

Test	PhEur 2005	USPNF 23
Identification	+	—
Characters	+	—
Melting range	30–45°C	27–44°C
Residue on ignition	—	⩽0.05%
Total ash	⩽0.05%	—
Acid value	⩽0.5	⩽1.0
Iodine value	⩽3.0	⩽7.0
Saponification value	210–260	215–255
Hydroxyl value	⩽50	⩽70
Peroxide value	⩽3.0	—
Unsaponifiable matter	⩽0.6%	⩽3.0%
Alkaline impurities	+	+
Heavy metals	⩽10 ppm	—

10 Typical Properties

Acid value: *see* Table III.

Color number:
⩽3 for *Massa estarinum* (iodine color index);
⩽3 for *Suppocire* excluding L grades (Gardener scale);
⩽5 for *Suppocire* L grades (Gardener scale);
⩽3 for *Witepsol* (iodine color index).

Density:
0.955–0.975 g/cm^3 for *Massa estarinum* at 20°C;
0.950–0.960 g/cm^3 for *Suppocire* at 20°C;
0.950–0.980 g/cm^3 for *Witepsol* at 20°C.

Heat of melting (22–40°C):
≈145 J/g/°C for *Massa estarinum*;
100–130 J/g/°C for *Suppocire*;
≈145 J/g/°C for *Witepsol.*

Hydroxyl value: *see* Table III.

Iodine value: *see* Table III.

Melting point: see Table III.

Moisture content:
⩽0.2% w/w for *Massa estarinum*;
<0.5% w/w for *Suppocire*;
⩽0.2% w/w for *Witepsol.*

Peroxide value:
⩽3 for *Massa estarinum*;
⩽1.2 for *Suppocire*;
⩽3 for *Witepsol.*

Saponification value: *see* Table III.

Solidification point: *see* Table III.

Solubility: freely soluble in carbon tetrachloride, chloroform, ether, toluene, and xylene; slightly soluble in warm ethanol; practically insoluble in water.

Specific heat:
≈2.6 J/g/°C for *Massa estarinum*;
1.7–2.5 J/g/°C for *Suppocire*;
≈2.6 J/g/°C for *Witepsol.*

Unsaponifiable matter: *see* Table III.

11 Stability and Storage Conditions

Hard fat suppository bases are fairly stable toward oxidation and hydrolysis, with the iodine value being a measure of their resistance to oxidation and rancidity. Water content is usually low and deterioration due to hygroscopicity rarely occurs.

Melting characteristics, hardness, and drug-release profiles alter with time, and the melting point may rise by more than 1.0°C after storage for several months. Owing to the complexity of bases, elucidation of the mechanisms that induce these changes on aging is difficult. Evidence has been presented(3) that supports a finite transition from amorphous to crystalline forms in which polymorphism may or may not contribute, whereas other workers have found melting point changes to be closely associated with the conversion of triglycerides to more stable polymorphic forms.(4) Before melting point determinations are made, bases are 'conditioned' to a stable crystalline form.

Suppository bases should be stored protected from light in an airtight container at a temperature at least 5°C less than their stated melting point. Refrigeration is usually recommended for molded suppositories.

Suppositories that are not effectively packaged may develop a 'bloom' of powdery crystals at the surface. This is usually due to the presence of high-melting-point components in the base and can often be overcome by using a different base. Alternatively, the base can be precrystallized prior to pouring, since the crystals will cause a quick and complete crystallization into its end crystal form. This process is called 'tempering.'

12 Incompatibilities

Incompatibilities with suppository bases are not now extensively reported in the literature. The occurrence of a chemical reaction between a hard fat suppository base and a drug is relatively rare, but any potential for such a reaction may be indicated by the magnitude of the hydroxyl value of the base. The risk of hydrolysis of aspirin, for example, may be reduced by the use of a base with a low hydroxyl value (<5) and,

Table III: Typical properties of suppository bases.

Product		Acid value	Hydroxyl value	Iodine value	Melting point (°C)	Saponification value	Solidification point (°C)	Unsaponifiable matter (%)
Cremao	CS-34	<0.3	—	<2	33–35	250	—	—
	CS-36	<0.3	—	<1	34–37	250	—	—
Massa Estarinum	B	≤0.3	20–30	≤3	33–35.5	225–240	31–33	≤0.3
	BC	≤0.3	30–40	≤3	33.5–35.5	225–240	30.5–32.5	≤0.3
	C	≤0.3	20–30	≤3	36–38	225–235	33–35	≤0.3
	299	≤0.3	≤2	≤3	33.5–35.5	240–255	32–34.5	≤0.3
Massupol	—	—	≤2	34–36	240–250	31–32.5	—	—
Massupol 15	—	—	≤3	35–37	220–230	31–33	—	—
Suppocire	A	<0.5	20–30	<2	35–36.5	225–245	—	≤0.5
	AM	<0.2	≤6	<2	35–36.5	225–245	—	≤0.5
	AML	<0.5	≤6	<2	35–36.5	225–245	—	≤0.6
	AIML	<0.5	≤6	<3	33–35	225–245	—	≤0.6
	AS$_2$	<0.5	15–25	<2	35–36.5	225–245	—	≤0.5
	AS$_2$X	<0.5	15–25	<2	35–36.5	225–245	—	≤0.6
	AT	<0.5	25–35	<2	35–36.5	225–245	—	≤0.5
	AP	<1.0	30–50	<1	33–35	200–220	—	≤0.5
	AI	<0.5	20–30	<2	33–35	225–245	—	≤0.5
	AIX	<0.5	20–30	<2	33–35	220–240	—	<0.6
	AIM	<0.3	<6	<2	33–35	225–245	—	≤0.5
	AIP	<1.0	30–50	<1	30–33	205–225	—	<0.5
	B	<0.5	20–30	<2	36–37.5	225–245	—	≤0.5
	BM	<0.2	<6	<2	36–37.5	225–245	—	≤0.5
	BML	<0.5	<6	<3	36–37.5	225–245	—	≤0.6
	BS$_2$	<0.5	15–25	<2	36–37.5	225–245	—	≤0.5
	BS$_2$X	<0.5	15–25	≤3	36–37.5	220–240	—	≤0.6
	BT	<0.5	25–35	<2	36–37.5	225–245	—	≤0.5
	BP	<1.0	30–50	<1	36–37	200–220	—	<0.5
	C	<0.5	20–30	<2	38–40	220–240	—	≤0.5
	CM	<0.2	<6	<2	38–40	225–245	—	≤0.5
	CS$_2$	<0.5	15–25	<2	38–40	220–240	—	≤0.5
	CS$_2$X	<0.5	15–25	<2	38–40	220–240	—	<0.6
	CT	<0.5	25–35	<2	38–40	220–240	—	≤0.5
	CP	<1.0	≤50	<1	37–39	200–220	—	<0.5
	D	<0.5	20–30	<2	42–45	215–235	—	≤0.5
	DM	<0.2	<6	<2	42–45	215–235	—	≤0.5
	NA	<0.5	<40	<2	35.5–37.5	225–245	—	<0.5
	NB	<0.5	<40	<2	36.5–38.5	215–235	—	<0.5
	NC	<0.5	<40	<2	38.5–40.5	220–240	—	<0.5
	NAI 0	<0.5	≤3	<2	33.5–35.5	220–245	—	<0.5
	NAI 5	<0.5	≤5	<2	33.5–35.5	220–245	—	<0.5
	NAI 10	<0.5	<15	<2	33.5–35.5	220–245	—	<0.5
	NAI	<0.5	<40	<2	33.5–35.5	225–245	—	<0.5
	NAIL	<1.0	<40	<3	33.5–35.5	225–245	—	<0.6
	NAIX	<0.5	<40	<2	33.5–35.5	220–240	—	<0.6
	NA 0	<0.5	≤3	<2	35.5–37.5	225–245	—	<0.5
	NA 5	<0.5	≤5	<2	35.5–37.5	225–245	—	<0.5
	NA 10	<0.5	≤15	<2	35.5–37.5	225–245	—	<0.5
	NAL	<0.5	<40	<2	33.5–35.5	225–245	—	<0.6
	NAX	<0.5	<40	<2	35.5–37.5	220–240	—	<0.6
	NBL	<0.5	<40	<3	36.5–38.5	220–240	—	<0.6
	NBX	<0.5	<40	<2	36.5–38.5	215–235	—	<0.6
	ND	<0.5	<40	<2	42–45	210–230	—	<0.5
Witepsol	H5	≤0.2	≤5	≤2	34–36	235–245	33–35	≤0.3
	H12	≤0.2	5–15	≤3	32–33.5	240–255	29–33	≤0.3
	H15	≤0.2	5–15	≤3	33.5–35.5	230–245	32.5–34.5	≤0.3
	H19[a]	≤0.2	20–30	≤7	33.5–35.5	230–240	—	≤0.3
	H32	≤0.2	≤3	≤3	31–33	240–250	30–32.5	≤0.3
	H35	≤0.2	≤3	≤3	33.5–35.5	240–250	32–35	≤0.3
	H37	≤0.2	≤3	≤3	36–38	225–245	35–37	≤0.3
	H175[a]	≤0.7	5–15	≤3	34.5–36.5	225–245	32–34.5	≤1.0
	H185	≤0.2	5–15	≤3	38–39	220–235	34–37	≤0.3

Continued

Table III: Continued

Product		Acid value	Hydroxyl value	Iodine value	Melting point (°C)	Saponification value	Solidification point (°C)	Unsaponifiable matter (%)
Witepsol (*cont.*)	W25	⩽0.3	20–30	⩽3	33.5–35.5	225–240	29–33	⩽0.3
	W31	⩽0.3	25–35	⩽3	35–37	225–240	30–33	⩽0.5
	W32	⩽0.3	40–50	⩽3	32–33.5	225–245	25–30	⩽0.3
	W35	⩽0.3	40–50	⩽3	33.5–35.5	225–235	27–32	⩽0.3
	W45	⩽0.3	40–50	⩽3	33.5–35.5	225–235	29–34	⩽0.3
	S51[a]	⩽1.0	55–70	⩽8	30–32	215–230	25–27	⩽2.0
	S52[a]	⩽1.0	50–65	⩽3	32–33.5	220–230	27–30	⩽2.0
	S55[a]	⩽1.0	50–65	⩽3	33.5–35.5	215–230	28–33	⩽2.0
	S58[a]	⩽1.0	60–70	⩽7	31.5–33	215–225	27–29	⩽2.0
	E75[a]	⩽1.3	5–15	⩽3	37–39	220–230	32–36	⩽3.0
	E76	⩽0.3	30–40	⩽3	37–39	220–230	31–35	⩽0.5
	E85	⩽0.3	5–15	⩽3	42–44	220–230	37–42	⩽0.5

[a] Note that these types are mixtures containing hard fat and therefore do not comply with the specifications of the PhEur 2005 and USPNF 23.

additionally, by minimization of the water content of both the base and the aspirin.

There is evidence that aminophylline reacts with the glycerides in some hard fat bases to form diamides. On aging or exposure to elevated temperatures, degradation is accompanied by hardening and suppositories tend to exhibit a marked increase in melting point. The ethylenediamine content is also reduced.(5,6)

Certain fat-soluble medications, such as chloral hydrate, may depress the melting point when incorporated into a base. Similarly, when large amounts of an active substance, either solid or liquid, have to be dispersed into a base, the rheological characteristics of the resultant suppository may be changed, with concomitant effects on release and absorption. Careful selection of bases or the inclusion of additives may therefore be necessary.

13 Method of Manufacture

The most common method of manufacture involves the hydrolysis of natural vegetable oils such as coconut or palm kernel oil, followed by fractional distillation of the free fatty acids produced. The C_8 to C_{18} fractions are then hydrogenated and reesterified under controlled conditions with glycerin to form a mixture of tri-, di-, and monoglycerides of the required characteristics and hydroxyl value. This process is used for *Witepsol*.

In an alternative procedure, coconut or palm kernel oil is directly hydrogenated and then subjected to an interesterification either with itself or with glycerin to form a mixture of tri-, di-, and monoglycerides of the required characteristics and hydroxyl value, e.g. *Suppocire*.

14 Safety

Suppository bases are generally regarded as nontoxic and nonirritant materials when used in rectal formulations. However, animal studies have suggested that some bases, particularly those types with a high hydroxyl value, may be irritant to the rectal mucosa.(7)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. There is a slight fire hazard on exposure to heat or flame.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (rectal and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Glycerin; medium-chain triglycerides; polyethylene glycol; theobroma oil.

Theobroma oil

CAS number: [8002-31-1]

Synonyms: cocoa butter; oleum cacao; oleum theobromatis.

Appearance: a yellowish or white, brittle solid with a slight odor of cocoa.

Melting point: 31–34°C

Solubility: freely soluble in chloroform, ether, and petroleum spirit; soluble in boiling ethanol; slightly soluble in ethanol (95%).

Stability and storage conditions: heating theobroma oil to more than 36°C during the preparation of suppositories can result in an appreciable lowering of the solidification point owing to the formation of metastable states; this may lead to difficulties in the setting of the suppository. Theobroma oil should be stored at a temperature not exceeding 25°C.

Comments: theobroma oil is a fat of natural origin used as a suppository base. It comprises a mixture of the triglycerides of saturated and unsaturated fatty acids, in which the unsaturated acid is preferentially situated on the 2-position of the glyceride. Theobroma oil is also a major ingredient of chocolate.

18 Comments

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21 Authors

RC Moreton.

22 Date of Revision

1 September 2005.

Talc

1 Nonproprietary Names

BP: Purified talc
JP: Talc
PhEur: Talcum
USP: Talc

2 Synonyms

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; *Luzenac Pharma*; magnesium hydrogen metasilicate; *Magsil Osmanthus*; *Magsil Star*; powdered talc; purified French chalk; *Purtalc*; soapstone; steatite; *Superiore*.

3 Chemical Name and CAS Registry Number

Talc [14807-96-6]

4 Empirical Formula and Molecular Weight

Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.

5 Structural Formula

See Section 4.

6 Functional Category

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent, *see* Table I,(1–3) although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products.(4–6) Talc is also used as a lubricant in tablet formulations;(7) in a novel powder coating for extended-release pellets;(8) and as an adsorbant.(9)

In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves; *see* Section 14. Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder; *see* Section 11.

Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

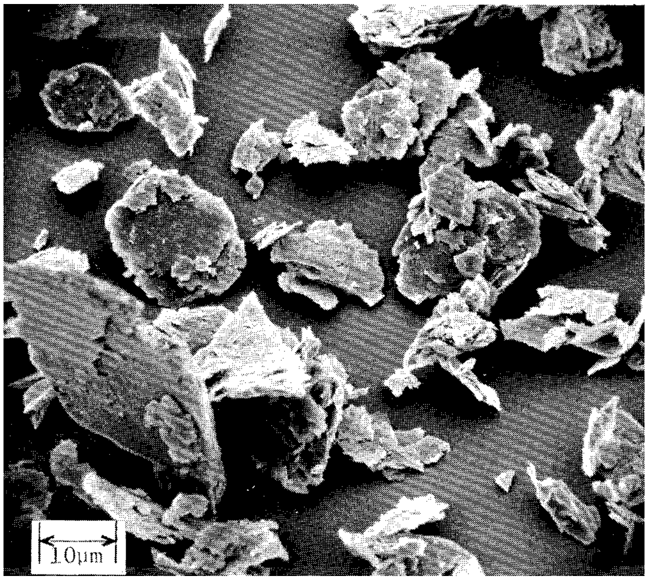
Table I: Uses of talc.

Use	Concentration (%)
Dusting powder	90.0–99.0
Glidant and tablet lubricant	1.0–10.0
Tablet and capsule diluent	5.0–30.0

8 Description

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

SEM: 1
Excipient: Talc (*Purtalc*)
Manufacturer: Charles B Chrystal Co., Inc.
Lot No.: 1102A-2
Magnification: 1200×
Voltage: 10 kV



9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Acidity/alkalinity: pH = 7–10 for a 20% w/v aqueous dispersion.

Hardness (Mohs): 1.0–1.5

Moisture content: talc absorbs insignificant amounts of water at 25°C and relative humidities up to about 90%.

Particle size distribution: varies with the source and grade of material. Two typical grades are $\geqslant$99% through a 74 μm (#200 mesh) or $\geqslant$99% through a 44 μm (#325 mesh).

Refractive index: n_D^{20} = 1.54–1.59

Solubility: practically insoluble in dilute acids and alkalis, organic solvents, and water.

Specific gravity: 2.7–2.8

Specific surface area: 2.41–2.42 m^2/g

Table II: Pharmacopeial specifications for talc.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	+	+	—
Acid-soluble substances	⩽2.0%	—	⩽2.0%
Acidity or alkalinity	—	+	—
Production	—	+	—
pH	—	7.0–9.0	—
Water-soluble substances	—	⩽0.2%	⩽0.1%
Aluminum	—	⩽2.0%	—
Calcium	—	⩽0.9%	—
Iron	—	⩽0.25%	—
Lead	—	⩽10 ppm	—
Magnesium	—	17.0–19.5	—
Loss on ignition	⩽5.0%	⩽7.0%	⩽6.5%
Microbial contamination	—	+	⩽500/g
Aerobic bacteria	—	⩽10^2/g	—
Fungi	—	⩽10^2/g	—
Acid and alkali-soluble substances	⩽4.0 mg	—	⩽2.0%
Water-soluble iron	+	—	+
Arsenic	⩽4 ppm	—	⩽3 ppm
Heavy metals	—	—	⩽0.004%
Lead	—	—	⩽0.001%

11 Stability and Storage Conditions

Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation.(10)

Talc should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatible with quaternary ammonium compounds.

13 Method of Manufacture

Talc is a naturally occurring hydropolysilicate mineral found in many parts of the world including Australia, China, Italy, India, France, and the USA.(11)

The purity of talc varies depending on the country of origin. For example, Italian types are reported to contain calcium silicate as the contaminant; Indian types contain aluminum and iron oxides; French types contain aluminum oxide; and American types contain calcium carbonate (California), iron oxide (Montana), aluminum and iron oxides (North Carolina), or aluminum oxide (Alabama).(12)

Naturally occurring talc is mined and pulverized before being subjected to flotation processes to remove various impurities such as asbestos (tremolite); carbon; dolomite; iron oxide; and various other magnesium and carbonate minerals. Following this process, the talc is finely powdered, treated with dilute hydrochloric acid, washed with water, and then dried. The processing variables of agglomerated talc strongly influence its physical characteristics.(13–15)

14 Safety

Talc is used mainly in tablet and capsule formulations. Talc is not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material. However, intranasal or intravenous abuse of products containing talc can cause granulomas in body tissues, particularly the lungs.(16–18) Contamination of wounds or body cavities with talc may also cause granulomas; therefore, it should not be used to dust surgical gloves. Inhalation of talc causes irritation and may cause severe respiratory distress in infants;(19) *see also* Section 15.

Although talc has been extensively investigated for its carcinogenic potential, and it has been suggested that there is an increased risk of ovarian cancer in women using talc, the evidence is inconclusive.(20,21) However, talc contaminated with asbestos has been proved to be carcinogenic in humans, and asbestos-free grades should therefore be used in pharmaceutical products.(22)

Also, long-term toxic effects of talc contaminated with large quantities of hexachlorophene caused serious irreversible neurotoxicity in infants accidentally exposed to the substance.(23)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Talc is irritant if inhaled and prolonged excessive exposure may cause pneumoconiosis.

In the UK, the occupational exposure limit for talc is 1 mg/m^3 of respirable dust long-term (8-hour TWA).(24) Eye protection, gloves, and a respirator are recommended.

16 Regulatory Status

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (buccal tablets; oral capsules and tablets; rectal and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Bentonite; magnesium aluminum silicate; magnesium silicate; magnesium trisilicate.

18 Comments

Various different grades of talc are commercially available that vary in their chemical composition depending upon their source and method of preparation.(11,25,26)

Talc derived from deposits that are known to contain associated asbestos is not suitable for pharmaceutical use. Tests for amphiboles and serpentines should be carried out to ensure that the product is free of asbestos. A specification for talc is contained in the Food Chemicals Codex (FCC).

The EINECS number for talc is 238-877-9.

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21 Authors

AH Kibbe.

22 Date of Revision

17 August 2005.

Tartaric Acid

1 Nonproprietary Names

BP: Tartaric acid
JP: Tartaric acid
PhEur: Acidum tartaricum
USPNF: Tartaric acid

2 Synonyms

L-(+)-2,3-Dihydroxybutanedioic acid; (2*R*,3*R*)-2,3-dihydroxybutane-1,4-dioic acid; 2,3-dihydroxysuccinic acid; E334; *d*-tartaric acid; L-(+)-tartaric acid.

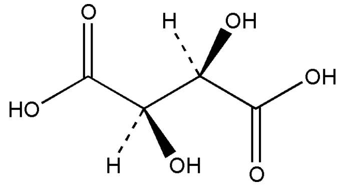
3 Chemical Name and CAS Registry Number

[*R*-(*R**,*R**)]-2,3-Dihydroxybutanedioic acid [87-69-4]

4 Empirical Formula and Molecular Weight

$C_4H_6O_6$ 150.09

5 Structural Formula



6 Functional Category

Acidifying agent; flavor enhancer; sequestering agent.

7 Applications in Pharmaceutical Formulation or Technology

Tartaric acid is used in beverages, confectionery, food products, and pharmaceutical formulations as an acidulant. It may also be used as a sequestering agent and as an antioxidant synergist. In pharmaceutical formulations, it is widely used in combination with bicarbonates, as the acid component of effervescent granules, powders, and tablets.

8 Description

Tartaric acid occurs as colorless monoclinic crystals, or a white or almost white crystalline powder. It is odorless, with an extremely tart taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for tartaric acid.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Appearance of solution	—	+	—
Specific rotation	—	+12.0° to +12.8°	+12.0° to +13.0°
Loss on drying	≤0.5%	≤0.2%	≤0.5%
Sulfated ash	—	≤0.1%	—
Residue on ignition	≤0.05%	—	≤0.1%
Organic volatile impurities	—	—	+
Chloride	—	≤100 ppm	—
Oxalic acid	—	≤350 ppm	—
Oxalate	+	—	+
Sulfate	≤0.048%	≤150 ppm	+
Calcium	+	≤200 ppm	—
Heavy metals	≤10 ppm	≤10 ppm	≤0.001%
Arsenic	≤1 ppm	—	—
Assay (dried basis)	≥99.7%	99.5–101.0%	99.7–100.5%

10 Typical Properties

Acidity/alkalinity: pH = 2.2 (1.5% w/v aqueous solution)
Density: 1.76 g/cm^3
Dissociation constant:
$pK_{a1} = 2.93$ at 25°C;
$pK_{a2} = 4.23$ at 25°C.
Heat of combustion: 1151 kJ/mol (275.1 kcal/mol)
Melting point: 168–170°C
Osmolarity: a 3.9% w/v aqueous solution is isoosmotic with serum.
Solubility: *see* Table II.
Specific heat: 1.20 J/g (0.288 cal/g) at 20°C
Specific rotation $[\alpha]_D^{20}$**:** +12.0° (20% w/v aqueous solution)

Table II: Solubility of tartaric acid.

Solvent	Solubility at 20°C unless otherwise stated
Chloroform	Practically insoluble
Ethanol (95%)	1 in 2.5
Ether	1 in 250
Glycerin	Soluble
Methanol	1 in 1.7
Propan-1-ol	1 in 10.5
Water	1 in 0.75 1 in 0.5 at 100°C

11 Stability and Storage Conditions

The bulk material is stable and should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Tartaric acid is incompatible with silver and reacts with metal carbonates and bicarbonates (a property exploited in effervescent preparations).

13 Method of Manufacture

Tartaric acid occurs naturally in many fruits as the free acid or in combination with calcium, magnesium, and potassium.

Commercially, L-(+)-tartaric acid is manufactured from potassium tartrate (cream of tartar), a by-product of wine making. Potassium tartrate is treated with hydrochloric acid, followed by the addition of a calcium salt to produce insoluble calcium tartrate. This precipitate is then removed by filtration and reacted with 70% sulfuric acid to yield tartaric acid and calcium sulfate.

14 Safety

Tartaric acid is widely used in food products and oral, topical, and parenteral pharmaceutical formulations. It is generally regarded as a nontoxic and nonirritant material, however, strong tartaric acid solutions are mildly irritant and if ingested undiluted may cause gastroenteritis.

An acceptable daily intake for L-(+)-tartaric acid has not been set by the WHO, although an acceptable daily intake of up to 30 mg/kg body-weight for monosodium L-(+)-tartrate has been established.(1)

LD_{50} (mouse, IV): 0.49 g/kg(2)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Tartaric acid may be irritant to the eyes; eye protection and rubber or plastic gloves are recommended. When heated to decomposition, tartaric acid emits acrid smoke and fumes.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IM and IV injections; oral solutions, syrups and tablets; sublingual tablets; topical films; rectal and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Citric acid monohydrate; fumaric acid; malic acid.

18 Comments

L-(+)-tartaric acid, the optical isomer usually encountered, is the naturally occurring form and is specified as tartaric acid in the PhEur 2005 and USPNF 23.

A specification for tartaric acid is contained in the Food Chemicals Codex (FCC). The EINECS number for tartaric acid is 205-105-7.

19 Specific References

1 FAO/WHO. Evaluation of certain food additives. Twenty-first report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1978; No. 617.
2 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 3349.

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21 Authors

KD Vaughan.

22 Date of Revision

13 August 2005.

Tetrafluoroethane (HFC)

1 Nonproprietary Names

None adopted.

2 Synonyms

Dymel 134a/P; fluorocarbon 134a; *Frigen 134a*; *Genetron 134a*; HFA 134a; HFC 134a; *Isceon 134a*; *Klea 134a*; propellant 134a; refrigerant 134a; *Solkane 134a*; *Suva 134a*; *Zephex 134a*.

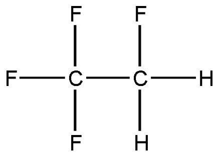
3 Chemical Name and CAS Registry Number

1,1,1,2-Tetrafluoroethane [811-97-2]

4 Empirical Formula and Molecular Weight

$C_2H_2F_4$ 102.0

5 Structural Formula



6 Functional Category

Aerosol propellant.

7 Applications in Pharmaceutical Formulation or Technology

Tetrafluoroethane is a hydrofluorocarbon (HFC) or hydrofluoroalkane (HFA) aerosol propellant (contains hydrogen, fluorine, and carbon) as contrasted to a CFC (chlorine, fluorine, and carbon). The lack of chlorine in the molecule and the presence of hydrogen reduces the ozone depletion activity to practically zero. Hence tetrafluoroethane can be considered as an alternative to CFCs in the formulation of metered-dose inhalers (MDIs).(1–9) It has replaced CFC-12 as a refrigerant since it has essentially the same vapor pressure. Its very low Kauri-butanol value and solubility parameter indicate that it is not a good solvent for the commonly used surfactants for MDIs. Sorbitan trioleate, sorbitan sesquioleate, oleic acid, and soya lecithin show limited solubility in tetrafluoroethane and the amount of surfactant that actually dissolves may not be sufficient to keep a drug readily dispersed.

When tetrafluoroethane (P-134a) is used for pharmaceutical aerosols and MDIs, the pharmaceutical grade must be specified. Industrial grades may not be satisfactory due to their impurity profiles.

8 Description

Tetrafluoroethane is a liquefied gas and exists as a liquid at room temperature when contained under its own vapor pressure, or as a gas when exposed to room temperature and atmospheric pressure. The liquid is practically odorless and colorless. The gas in high concentrations has a slight etherlike odor. Tetrafluoroethane is noncorrosive, nonirritating, and nonflammable.

9 Pharmacopeial Specifications

—

10 Typical Properties

Boiling point: −26.2°C
Critical pressure: 4.11 MPa (40.55 atm)
Critical temperature: 101.0°C
Density:
1.226 g/cm^3 for liquid at 20°C;
1.207 g/cm^3 for liquid at 25°C.
Flammability: nonflammable.
Freezing point: −108°C
Kauri-butanol value: 8
Solubility: soluble in ethanol (95%), ether, and 1 in 1294 parts of water at 20°C.
Surface tension: 8.6 kN/m
Vapor density (absolute): 4.466 g/cm^3 at standard temperature and pressure.
Vapor density (relative): 3.53 (air = 1)
Vapor pressure:
569 kPa at 20°C;
662 kPa at 25°C.
Viscosity (dynamic):
0.222 mPa s (0.222 cP) for liquid at 20°C;
0.210 mPa s (0.210 cP) for liquid at 25°C.

11 Stability and Storage Conditions

Tetrafluoroethane is a nonreactive and stable material. The liquified gas is stable when used as a propellant and should be stored in a metal cylinder in a cool dry place.

12 Incompatibilities

The major incompatibility of tetrafluoroethane is its lack of miscibility with water. Since it has a very low Kauri-butanol value, tetrafluoroethane is considered to be a very poor solvent for most drugs used in MDI formulations. It also shows a low solubility for some of the commonly used MDI surfactants.

13 Method of Manufacture

Tetrafluoroethane can be prepared by several different routes; however, the following routes of preparation illustrate the methods used:

Isomerization/hydrofluorination of 1,1,2-trichloro-1,2,2-trifluoroethane (CFC-113) to 1,1-dichloro-1,2,2,2-tetrafluoroethane (CFC-114a), followed by hydrodechlorination of the latter.

Hydrofluorination of trichloroethylene, via 1-chloro-1,1,1-trifluoroethane (HCFC-133a).

14 Safety

Tetrafluoroethane is used as a refrigerant and as a non-CFC propellant in various aerosols including pharmaceuticals (MDIs). Tetrafluoroethane is regarded as nontoxic and non-irritating when used as directed. No acute or chronic hazard is present when exposures to the vapor are below the acceptable exposure limit (AEL) of 1000 ppm, 8-hour and 12-hour time weighed average (TWA).(10) In this regard it has the same value as the threshold limit value (TLV) for CFC-12. Inhaling a high concentration of tetrafluoroethane vapors can be harmful and is similar to inhaling vapors of CFC-12. Intentional inhalation of vapors of tetrafluoroethane can be dangerous and may cause death. The same labeling required on CFC aerosols would be required for those containing tetrafluoroethane as a propellant (except for the EPA requirement). *See* Chlorofluorocarbons, Section 14.

15 Handling Precautions

Tetrafluoroethane is usually encountered as a liquefied gas and appropriate precautions for handling should be taken. Eye protection, gloves, and protective clothing are recommended. Tetrafluoroethane should be handled in a well-ventilated environment. The vapors are heavier than air and do not support life; therefore, when cleaning large tanks that have contained the propellant, adequate provisions for oxygen supply in the tanks must be made in order to protect workers cleaning the tanks.

Although nonflammable, when heated to decomposition tetrafluoroethane emits toxic fumes.

In the UK, the long-term exposure limit (8-hour TWA) for tetrafluoroethane is 4240 mg/m^3 (1000 ppm).(11)

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (aerosol formulations for inhalation and nasal applications). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Difluoroethane; heptafluoropropane.

18 Comments

The use of tetrafluoroethane as a propellant for MDIs has been the subject of numerous patents throughout the world. These patents cover the formulation of MDIs and use of specific surfactants, cosolvents, etc. A US patent claims a self-propelling aerosol formulation that may be free of CFCs and which comprises a medicament, 1,1,1,2-tetrafluoroethane, a surface-active agent, and at least one compound having a higher polarity than 1,1,1,2-tetrafluoroethane.(12) Another patent has been issued by the European Patent Office and has 14 claims, among them a claim that includes tetrafluoroethane, an alcohol (such as ethanol), surfactant, and medicament.(13) The formulator is referred to the patent literature prior to formulating a MDI with tetrafluoroethane as the propellant. The formulation of MDI with this non-CFC propellant is complicated since tetrafluoroethane serves as a replacement for dichlorodifluoromethane or dichlorotetrafluoroethane. The use of an HFC as the propellant also requires a change in manufacturing procedure, which necessitates a redesign of the filling and packaging machinery for a MDI.(14)

Currently, there are no pharmacopeial specifications for tetrafluoroethane. However, typical specifications are shown in Table I.

Table I: Typical product specifications for tetrafluoroethane.

Test	Value
Appearance	Clear and colorless
High boiling impurities	$\leqslant$0.01%
Acidity as HCl	$\leqslant$0.1 ppm
Non-volatile residue	$\leqslant$5 ppm
Non-absorbable gases	$\leqslant$1.5%
Water	$\leqslant$10 ppm
Total unidentified impurities	$\leqslant$10 ppm
Assay	$\geqslant$99.99%

19 Specific References

1 Strobach DR. Alternative to CFCs. *Aerosol Age* 1988; **33**(7): 32–33, 42–43.
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21 Authors

CJ Sciarra, JJ Sciarra.

22 Date of Revision

21 August 2005.

Thaumatin

1 Nonproprietary Names

None adopted.

2 Synonyms

E957; *Talin*; taumatin; thalin; thaumatine; thaumatins; thaumatins protein.

3 Chemical Name and CAS Registry Number

Thaumatin [53850-34-3]

4 Empirical Formula and Molecular Weight

See Section 5.

5 Structural Formula

Thaumatin is a mixture of five thaumatin proteins; thaumatins I, II, III, and a and b; where thaumatins I and II predominate. Thaumatins I and II consist of almost identical sequences of amino acids. There are no unusual side-chains or peptide linkages, and there are no end-group substitutions.

6 Functional Category

Flavor enhancer; sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

Thaumatin is a naturally occurring intense sweetening agent approximately 2000–3000 times as sweet as sucrose. It has a delayed-onset taste profile and long (up to one hour) licorice-like aftertaste. It is used extensively in food applications as a sweetening agent and flavor enhancer and has potential for use in pharmaceutical applications such as oral suspensions.(1) The typical level used in foods is 0.5–3 ppm, although higher levels are used in certain applications such as chewing gum. Synergistic effects with other intense sweeteners such as acesulfame K and saccharin occur. The extensive disulfide crosslinking within thaumatin maintains the tertiary structure of the polypeptide: cleavage of just one disulfide bridge has been shown to result in the loss of the sweet taste of thaumatin.(2)

8 Description

Thaumatin occurs as a pale-brown colored, odorless, hygroscopic powder with an intensely sweet taste.

9 Pharmacopeial Specifications

—

10 Typical Properties

Solubility: *see* Table I.

Table I: Solubility of thaumatin

Solvent	Solubility at 25°C unless otherwise stated
Acetone	Practically insoluble
Ethanol (95%)	Soluble
Glycerin	Soluble
Propylene glycol	Soluble
Water	1 in 5 at pH 3

11 Stability and Storage Conditions

Thaumatin is stable in aqueous solutions at pH 2–8. It is also heat-stable at less than pH 5.5 (e.g., during baking, canning, pasteurizing, or UHT processes).

12 Incompatibilities

—

13 Method of Manufacture

Thaumatin is a naturally occurring intense sweetener isolated from the fruit of the African plant *Thaumatococcus daniellii* (Benth).(3) Commercially, thaumatin is produced by aqueous extraction under reduced pH conditions followed by other physical processes such as reverse osmosis.

14 Safety

Thaumatin is accepted for use in food products either as a sweetener or as a flavor modifier in a number of areas including Europe and Australia. It is also used in oral hygiene products such as mouthwashes and toothpastes and has been proposed for use in oral pharmaceutical formulations. Thaumatin is generally regarded as a relatively nontoxic and nonirritant material when used as an excipient. In Europe, because of its lack of toxicity, an ADI has been set of 'not specified'.(4,5)

LD_{50} (mouse, oral): >20 g/kg(5)
LD_{50} (rat, oral): >20 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in nonparenteral medicines licensed in the UK.

17 Related Substances

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18 Comments

As thaumatin is a protein it has some calorific value; however, in food products and pharmaceutical formulations the quantities used are so small that the calorific value is insignificant.

The EINECS number for thaumatin is 258-822-2.

19 Specific References

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4 Higginbotham JD, Snodin DJ, Eaton KK, Daniel JW. Safety evaluation of thaumatin (Talin Protein). *Food Chem Toxicol* 1983; **21**(6): 815–823.

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20 General References

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21 Authors

PJ Weller.

22 Date of Revision

23 May 2005.

Thimerosal

1 Nonproprietary Names

BP: Thiomersal
PhEur: Thiomersalum
USP: Thimerosal

2 Synonyms

[(*o*-Carboxyphenyl)thio]ethylmercury sodium salt; ethyl (2-mercaptobenzoato-*S*)-mercury, sodium salt; ethyl (sodium *o*-mercaptobenzoato)mercury; mercurothiolate; sodium ethylmercurithiosalicylate; *Thimerosal Sigmaultra*; thiomersalate.

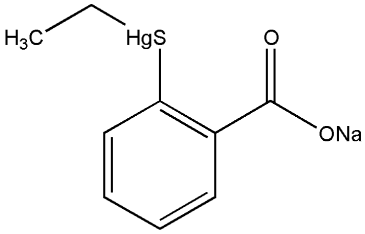
3 Chemical Name and CAS Registry Number

Ethyl[2-mercaptobenzoato(2–)-*O*,*S*]-mercurate(1–) sodium [54-64-8]

4 Empirical Formula and Molecular Weight

$C_9H_9HgNaO_2S$ 404.81

5 Structural Formula



6 Functional Category

Antimicrobial preservative; antiseptic.

7 Applications in Pharmaceutical Formulation or Technology

Thimerosal has been used as an antimicrobial preservative in biological and pharmaceutical preparations since the 1930s;(1) *see* Table I.

It is used as an alternative to benzalkonium chloride and other phenylmercuric preservatives and has both bacteriostatic and fungistatic activity. Increasing concerns over its safety have, however, led to questions regarding its continued use in formulations; *see* Section 14.

Thimerosal is also used in cosmetics (*see* Section 16) and to preserve soft contact lens solutions.

Therapeutically, thimerosal is occasionally used as a bacteriostatic and fungistatic mercurial antiseptic, which is usually applied topically at a concentration of 0.1% w/w.(2) However, its use is declining owing to its toxicity and effects on the environment.

8 Description

Thimerosal is a light cream-colored crystalline powder with a slight, characteristic odor.

Table I: Uses of thimerosal.

Use	Concentration (%)
IM, IV, SC injections	0.01
Ophthalmic solutions	0.001–0.15
Ophthalmic suspensions	0.001–0.004
Otic preparations	0.001–0.01
Topical preparations	0.01

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for thimerosal.

Test	PhEur 2005 (Suppl. 5.1)	USP 28
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Melting point	103–105°C	—
pH	6.0–8.0	—
Inorganic mercury compounds	⩽0.70%	—
Loss of drying	⩽0.5%	⩽0.5%
Ether-soluble substances	—	⩽0.8%
Mercury ions	—	⩽0.70%
Readily carbonizable substances	—	+
Assay	97.0–101.0%	97.0–101.0%

10 Typical Properties

Acidity/alkalinity: pH = 6.7 for a 1% w/v aqueous solution at 20°C.

Antimicrobial activity: thimerosal is bactericidal at acidic pH, bacteriostatic and fungistatic at alkaline or neutral pH. Thimerosal is not effective against spore-forming organisms. *See also* Section 12. For reported minimum inhibitory concentrations (MICs), *see* Table III.(3)

Table III: Reported minimum inhibitory concentrations (MICs) for thimerosal.(3)

Microorganism	MIC (μg/mL)
Aspergillus niger	128.0
Candida albicans	32.0
Escherichia coli	4.0
Klebsiella pneumoniae	4.0
Penicillium notatum	128.0
Pseudomonas aeruginosa	8.0
Pseudomonas cepacia	8.0
Pseudomonas fluorescens	4.0
Staphylococcus aureus	0.2

Density (bulk): $<0.33\,g/cm^3$
Dissociation constant: $pK_a = 3.05$ at 25°C.
Melting point: 232–233°C with decomposition.
Solubility: soluble 1 in 8 of ethanol (95%), 1 in 1 of water; practically insoluble in benzene and ether.

11 Stability and Storage Conditions

Thimerosal is stable at normal temperatures and pressures; exposure to light may cause discoloration.

Aqueous solutions may be sterilized by autoclaving but are sensitive to light. The rate of oxidation in solutions is increased by the presence of trace amounts of copper and other metals. Edetic acid or edetates may be used to stabilize solutions but have been reported to reduce the antimicrobial efficacy of thimerosal solutions; *see* Section 12.

The solid material should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

Incompatible with aluminum and other metals, strong oxidizing agents, strong acids and bases, sodium chloride solutions,(4) lecithin, phenylmercuric compounds, quaternary ammonium compounds, thioglycolate, and proteins. The presence of sodium metabisulfite, edetic acid, and edetates in solutions can reduce the preservative efficacy of thimerosal.(5)

In solution, thimerosal may be adsorbed by plastic packaging materials, particularly polyethylene. It is strongly adsorbed by treated or untreated rubber caps that are in contact with solutions.(6,7)

When it was used with cyclodextrin, the effectiveness of thimerosal was reduced; however, this was related to the lipid nature of the other ingredients in the preparation.(8)

13 Method of Manufacture

Thimerosal is prepared by the interaction of ethylmercuric chloride, or hydroxide, with thiosalicylic acid and sodium hydroxide, in ethanol (95%).

14 Safety

Thimerosal is widely used as an antimicrobial preservative in parenteral and topical pharmaceutical formulations. However, concern over the use of thimerosal in pharmaceuticals has increased as a result of a greater awareness of the toxicity of mercury and other associated mercury compounds.(9,10) The increasing number of reports of adverse reactions, particularly hypersensitivity,(11,12) to thimerosal and doubts as to its effectiveness as a preservative have led to suggestions that it should not be used as a preservative in eye drops(13) or vaccines.(14–16) In both Europe and the USA, regulatory bodies have recommended that thimerosal in vaccines be phased out.(17–19)

More recent studies assessing the safety of thimerosal in vaccines have however suggested that while the risk of hypersensitivity reactions is present, the relative risk of neurological harm in infants is negligible given the quantities of thimerosal present in vaccines.(20–22) Regulatory bodies in Europe and the USA have therefore updated their advice on the use of thimerosal in vaccines by stating that while it would be desirable for thimerosal to not be included in vaccines and other formulations the benefits of vaccines far outweigh any risks of adverse effects associated with their use.(23,24)

The most frequently reported adverse reaction to thimerosal, particularly in vaccines,(14–27) is hypersensitivity, usually with erythema and papular or vesicular eruptions. Although not all thimerosal-sensitive patients develop adverse reactions to vaccines containing thimerosal, there is potential risk. Patch testing in humans and animal experiments have suggested that 0.1% w/v thimerosal can sensitize children.(28) The incidence of sensitivity to thimerosal appears to be increasing; a study of 256 healthy subjects showed approximately 6% with positive sensitivity.(29)

Adverse reactions to thimerosal used to preserve contact lens solutions have also been reported. Reactions include ocular redness, irritation, reduced lens tolerance, and conjunctivitis.(30–32) One estimate suggests that approximately 10% of contact lens wearers may be sensitive to thimerosal.(33)

Thimerosal has also been associated with false positive reactions to old tuberculin,(34) ototoxicity,(35) and an unusual reaction to aluminum(36) in which a patient suffered a burn 5 cm in diameter at the site of an aluminum foil diathermy electrode after preoperative preparation of the skin with a 0.1% w/v thimerosal solution in ethanol (50%). Investigation showed that considerable heat was generated when such a solution came into contact with aluminum.

An interaction between orally administered tetracyclines and thimerosal, which resulted in varying extents of ocular irritation, has been reported in patients using a contact lens solution preserved with thimerosal.(37)

Controversially, some have claimed a connection between the use of thimerosal in vaccines and the apparent rise in the incidence of autism. However, recent studies have shown no association between thimerosal exposure and autism.(38,39)

LD_{50} (mouse, oral): 91 mg/kg(40)
LD_{50} (rat, oral): 75 mg/kg
LD_{50} (rat, SC): 98 mg/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Thimerosal is irritant to the skin and mucous membranes and may be systemically absorbed through the skin and upper respiratory tract. Thimerosal should be handled in a well-ventilated environment. Eye protection, gloves, and a respirator are recommended.

Chemical decomposition may cause the release of toxic fumes containing oxides of carbon, sulfur, and mercury in addition to mercury vapor. In the UK, the occupational exposure limit for mercury-containing compounds, calculated as mercury, is $0.01\,mg/m^3$ long-term (8-hour TWA) and $0.03\,mg/m^3$ short-term.(41)

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IM, IV, and SC injections; ophthalmic, otic, and topical preparations). Included in nonparenteral and parenteral medicines licensed in the UK. In the UK, the use of thimerosal in cosmetics is limited to 0.003% w/w (calculated as mercury) as a preservative in shampoos and hair-creams, which contain nonionic emulsifiers that would render other preservatives ineffective. The total permitted concentration (calculated as mercury) when mixed with other mercury compounds is 0.007% w/w.(42) Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Phenylmercuric acetate; phenylmercuric borate; phenylmercuric nitrate.

18 Comments

Some variation between the results obtained when comparing different thimerosal assay methods has been reported.(43)

The EINECS number for thimerosal is 200-210-4.

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21 Authors

PJ Weller.

22 Date of Revision

13 April 2005.

Thymol

1 Nonproprietary Names

BP: Thymol
PhEur: Thymolum
USPNF: Thymol

2 Synonyms

Acido trimico; 3-*p*-cymenol; *p*-cymen-3-ol; *Flavinol*; 3-hydroxy-*p*-cymene; 3-hydroxy-1-methyl-4-isopropylbenzene; *Intrasol*; isopropyl cresol; isopropyl-*m*-cresol; 6-isopropyl-*m*-cresol; isopropyl metacresol; 2-isopropyl-5-methylphenol; 1-methyl-3-hydroxy-4-isopropylbenzene; 5-methyl-2-isopropylphenol; 5-methyl-2-(1-methylethyl) phenol; *Medophyll*; thyme camphor; thymic acid; *m*-thymol; timol.

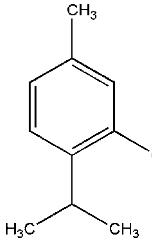
3 Chemical Name and CAS Registry Number

Thymol [89-83-8]

4 Empirical Formula and Molecular Weight

$C_{10}H_{14}O$ 150.24

5 Structural Formula



6 Functional Category

Antioxidant; antiseptic; cooling agent; disinfectant; flavoring agent; skin penetrant; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Thymol is a phenolic antiseptic, which has antibacterial and antifungal activity. However, it is not suitable for use as a preservative in pharmaceutical formulations because of its low aqueous solubility. The antimicrobial activity of thymol against eight oral bacteria has been studied *in vitro*. Inhibitory activity was noted against almost all organisms, and a synergistic effect was observed for combinations of thymol and eugenol and of thymol and carvacrol.(1) The activity of thymol against bacteria commonly involved in upper respiratory tract infections has also been shown.(2)

Thymol is a more powerful disinfectant than phenol, but its low water solubility, its irritancy to tissues, and its inactivation by organic material, such as proteins, limit its use as a disinfectant. Thymol is chiefly used as a deodorant in antiseptic mouthwashes, gargles, and toothpastes, such as in Compound Thymol Glycerin BP, in which it has no antiseptic action.

Thymol is also a true antioxidant and has been used at concentrations of 0.01% as an antioxidant for halothane, trichloroethylene, and tetrachloroethylene.

More recently, thymol has been shown to enhance the *in vitro* percutaneous absorption of a number of drugs, including 5-fluorouracil,(3) piroxicam,(4) propranolol,(5) naproxen,(6) and tamoxifen.(7) Studies have also demonstrated that the melting point of lidocaine is significantly lowered when it is mixed with thymol.(8,9)

The inhalation of thymol, in combination with other volatile substances, is used to alleviate the symptoms of colds, coughs, and associated respiratory disorders. Externally, thymol has been used in dusting powders for the treatment of fungal skin infections. Thymol was formerly used in the treatment of hookworm infections but has now been superseded by less toxic substances.

In dentistry, thymol has been mixed with phenol and camphor to prepare cavities before filling, and mixed with zinc oxide to form a protective cap for dentine.

Thymol has been included in food, perfume, and cosmetic products, and has also been used as a pesticide and fungicide.

8 Description

Thymol occurs as colorless or often large translucent crystals, or as a white crystalline powder with a herbal odor (aromatic and thyme-like) and a pungent caustic taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for thymol.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Melting range	48–52°C	48–51°C
Appearance of solution	+	—
Acidity	+	—
Related substances	+	—
Residue on evaporation	⩽0.05%	⩽0.05%
Organic volatile impurities	—	+
Assay	—	99.0–101.0%

10 Typical Properties

Acidity/alkalinity: a 4% solution in ethanol (50%) is neutral to litmus.

Boiling point: about 233°C

Density: 0.97 g/cm^3 at 25°C; has a greater density than water, but when liquefied by fusion is less dense than water.

Dissociation constant: $pK_a = 10.6$ at 20°C

Melting point: 48–51°C, but, once melted, remains liquid at a considerably lower temperature.

Partition coefficient: log (octanol–water) = 3.3
Phenol coefficient: about 50
Refractive index:
n_{D}^{25} = 0.15204;
n_{D}^{20} = 0.15227.
Solubility: soluble 1 in 0.7–1.0 of chloroform, 1 in 1 of ethanol (95%), 1 in 1.5 of ether, glacial acetic acid, 1 in 1.7–2.0 of olive oil, 1 in 1000 of water. Freely soluble in essential oils, fixed oils, and fats. Sparingly soluble in glycerin. Dissolves in dilute solutions of alkali hydroxides, forming salts that have increased solubility but whose solutions darken on standing.
Vapor pressure: 0.04 mmHg at 20°C
Volatility appreciable volatility at 100°C; volatile in water vapor at 25°C.

11 Stability and Storage Conditions

Thymol should be stored in well-closed, light-resistant containers, in a cool, dry, place. Thymol is affected by light.

12 Incompatibilities

Thymol is incompatible with iodine, alkalis, and oxidizing agents. It liquefies, or forms soft masses, on trituration with acetanilide, antipyrine, camphor, monobromated camphor, chloral hydrate, menthol, phenol, or quinine sulfate.

13 Method of Manufacture

Thymol is obtained from the volatile oil of thyme (*Thymus vulgaris* Linne (Fam Labiatae)) by fractional distillation followed by extraction and recrystallization. Thyme oil yields about 20–30% thymol. Thymol may also be produced synthetically from *p*-cymene, menthone, or piperitone, or by the interaction of *m*-cresol with isopropyl chloride.

14 Safety

Thymol is used in cosmetics, foods, and pharmaceutical applications as an excipient. However, thymol may be irritating when inhaled or following contact with the skin or eyes. It may also cause abdominal pain and vomiting, and sometimes stimulation followed by depression of the central nervous system following oral consumption.

Respiratory arrest, attributed to acute nasal congestion and edema, has been reported in a 3-week-old patient due to the erroneous intranasal application of *Karvol*, a combination product that includes thymol. The patient recovered, but it was recommended that inhalation decongestants should not be used in children under the age of 5 years.(10)

LD_{50} (guinea pig, oral): 0.88 g/kg(11)
LD_{50} (mouse, IP): 0.11 g/kg
LD_{50} (mouse, IV): 0.1 g/kg
LD_{50} (mouse, oral): 0.64 g/kg
LD_{50} (mouse, SC): 0.243 g/kg
LD_{50} (rat, oral): 0.98 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Special precautions should be taken to avoid inhalation, or contact with the skin or eyes. Eye protection and gloves are recommended. When thymol is heated to decomposition, carbon dioxide and carbon monoxide are formed.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (inhalation, liquid; oral, powder for solution). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Menthol.

18 Comments

The EINECS number for thymol is 201-944-8.

19 Specific References

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20 General References

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21 Authors

CG Cable.

22 Date of Revision

19 August 2005.

Titanium Dioxide

1 Nonproprietary Names

BP: Titanium dioxide
JP: Titanium oxide
PhEur: Titanii dioxidum
USP: Titanium dioxide

2 Synonyms

Anatase titanium dioxide; brookite titanium dioxide; color index number 77891; E171; *Kronos 1171*; pigment white 6; rutile titanium dioxide; *Tioxide*; *TiPure*; titanic anhydride; *Tronox*.

3 Chemical Name and CAS Registry Number

Titanium oxide [13463-67-7]

4 Empirical Formula and Molecular Weight

TiO_2 79.88

5 Structural Formula

TiO_2

6 Functional Category

Coating agent; opacifier; pigment.

7 Applications in Pharmaceutical Formulation or Technology

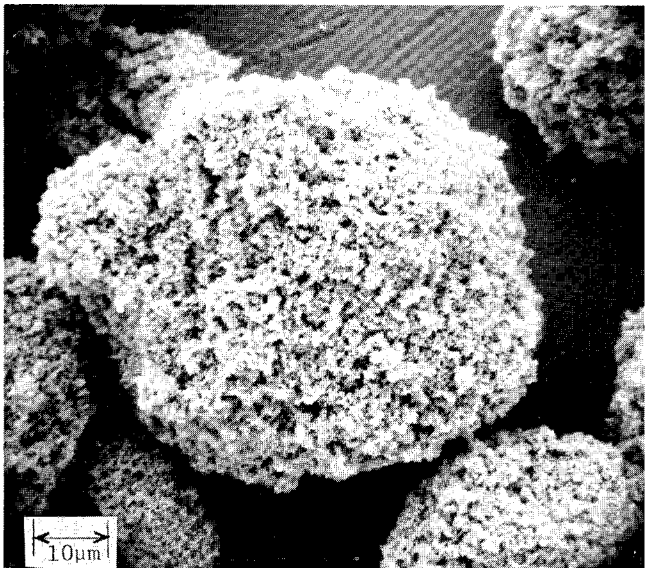
Titanium dioxide is widely used in confectionery, cosmetics, and foods, in the plastics industry, and in topical and oral pharmaceutical formulations as a white pigment.

Owing to its high refractive index, titanium dioxide has light-scattering properties that may be exploited in its use as a white pigment and opacifier. The range of light that is scattered can be altered by varying the particle size of the titanium dioxide powder. For example, titanium dioxide with an average particle size of 230 nm scatters visible light, while titanium dioxide with an average particle size of 60 nm scatters ultraviolet light and reflects visible light.(1)

In pharmaceutical formulations, titanium dioxide is used as a white pigment in film-coating suspensions,(2,3) sugar-coated tablets, and gelatin capsules. Titanium dioxide may also be admixed with other pigments.

Titanium dioxide is also used in dermatological preparations and cosmetics, such as sunscreens.(1,4)

SEM: 1
Excipient: Titanium dioxide
Magnification: 1200×
Voltage: 10 kV



8 Description

White, amorphous, odorless, and tasteless nonhygroscopic powder. Although the average particle size of titanium dioxide powder is less than 1 μm, commercial titanium dioxide generally occurs as aggregated particles of approximately 100 μm diameter.

Titanium dioxide may occur in several different crystalline forms: rutile; anatase; and brookite. Of these, rutile and anatase are the only forms of commercial importance. Rutile is the more thermodynamically stable and is used more frequently than the other crystalline forms.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Density (bulk): 0.4–0.62 g/cm^{3}(5)
Density (tapped): 0.625–0.830 g/cm^{3}(6)
Density (true):
3.8–4.1 g/cm^3 for Anatase;
3.9–4.2 g/cm^3 for Rutile.
Dielectric constant:
48 for Anatase;
114 for Rutile.
Hardness (Mohs):
5–6 for Anatase;
6–7 for Rutile.
See also Section 18.
Melting point: 1855°C

Table I: Pharmacopeial specifications for titanium dioxide.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	—	+	—
Appearance of solution	—	+	—
Acidity or alkalinity	—	+	—
Water-soluble substances	≤5.0 mg	≤25 mg	≤0.25%
Antimony	—	+	—
Arsenic		≤10 ppm	≤5 ppm
≤1 ppm			
Barium	—	+	—
Heavy metals	—	≤20 ppm	—
Iron	—	+	—
Loss on drying	≤0.5%	—	≤0.5%
Loss on ignition	—	—	≤13%
Acid-soluble substances	—	—	≤0.5%
Organic volatile impurities	—	—	+
Lead		≤60 ppm	—
—			
Assay	≥98.5%	98.0–100.5%	99.0–100.5%

Moisture content: 0.44%

Particle size distribution: average particle size = 1.05 μm.[5] *See also* Figures 1 and 2.

Refractive index:
2.55 for Anatase;
2.76 for Rutile.

Specific heat:
0.71 J/g (0.17 cal/g) for Anatase;
0.71 J/g (0.17 cal/g) for Rutile.

Specific surface area: 9.90–10.77 m^2/g

Solubility: practically insoluble in dilute sulfuric acid, hydrochloric acid, nitric acid, organic solvents, and water. Soluble in hydrofluoric acid and hot concentrated sulfuric acid. Solubility depends on previous heat treatment; prolonged heating produces a less-soluble material.

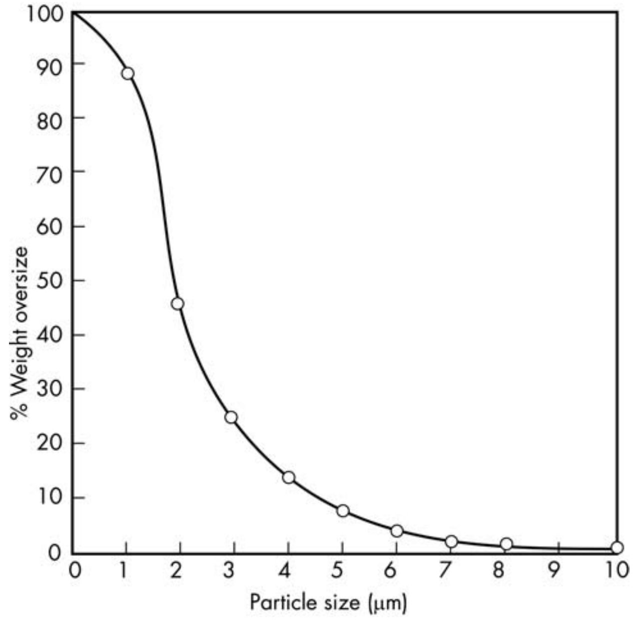


Figure 1: Particle-size distribution of titanium dioxide (fine powder).

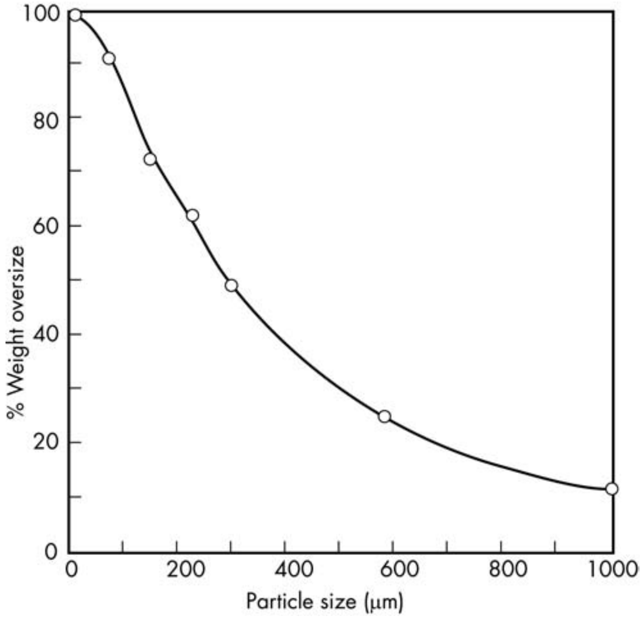


Figure 2: Particle-size distribution of titanium dioxide (agglomerated particles).

Tinting strength (Reynolds):
1200–1300 for Anatase;
1650–1900 for Rutile.

11 Stability and Storage Conditions

Titanium dioxide is extremely stable at high temperatures. This is due to the strong bond between the tetravalent titanium ion and the bivalent oxygen ions. However, titanium dioxide can lose small, unweighable amounts of oxygen by interaction with radiant energy. This oxygen can easily recombine again as a part of a reversible photochemical reaction, particularly if there is no oxidizable material available. These small oxygen losses are important because they can cause significant changes in the optical and electrical properties of the pigment.

Titanium dioxide should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

Owing to a photocatalytic effect, titanium dioxide may interact with certain active substances, e.g. famotidine.[7] Studies have shown that titanium dioxide monatonically degrades film mechanical properties and increases water vapor permeability of polyvinyl alcohol coatings when used as an inert filler and whitener.[6]

Titanium dioxide has also been shown to induce photooxidation of unsaturated lipids.[8]

13 Method of Manufacture

Titanium dioxide occurs naturally as the minerals rutile (tetragonal structure), anatase (tetragonal structure), and brookite (orthorhombic structure).

Titanium dioxide may be prepared commercially by direct combination of titanium and oxygen; by treatment of titanium salts in aqueous solution; by the reaction of volatile inorganic titanium compounds with oxygen; and by the oxidation or hydrolysis of organic compounds of titanium.

14 Safety

Titanium dioxide is widely used in foods and oral and topical pharmaceutical formulations. It is generally regarded as an essentially nonirritant and nontoxic excipient.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended. Titanium dioxide is regarded as a relatively innocuous nuisance dust,(9) that may be irritant to the respiratory tract. In the UK, the long-term (8-hour TWA) exposure limit is 10 mg/m^3 for total inhalable dust and 4 mg/m^3 for respirable dust.(10)

Titanium dioxide particles in the 500 nm range have been reported to translocate to all major body organs after oral administration in the rat.(11)

16 Regulatory Status

Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (dental paste; intrauterine suppositories; ophthalmic preparations; oral capsules, suspensions, tablets; topical and transdermal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Coloring agents.

18 Comments

Titanium dioxide is a hard, abrasive material. Coating suspensions containing titanium dioxide have been reported to cause abrasion and wear of a steel-coated pan surface, which led to white tablets being contaminated with black specks.(12)

If titanium dioxide is used as a pigment it should conform to the appropriate food standards specifications, which are more demanding than the pharmacopeial specifications.

When mixed with methylcellulose, titanium dioxide can reduce the elongation and tensile strength of the film but slightly increase the adhesion between pigmented film and the tablet surface.(13) A specification for titanium dioxide is contained in the Food Chemicals Codex (FCC).

The EINECS number for titanium dioxide is 236-675-5.

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PJ Weller.

22 Date of Revision

13 April 2005.

Tragacanth

1 Nonproprietary Names

BP: Tragacanth
JP: Tragacanth
PhEur: Tragacantha
USPNF: Tragacanth
See also Section 18.

2 Synonyms

E413; goat's thorn; gum benjamin; gum dragon; gum tragacanth; persian tragacanth; trag; tragant.

3 Chemical Name and CAS Registry Number

Tragacanth gum [9000-65-1]

4 Empirical Formula and Molecular Weight

Tragacanth is a naturally occurring dried gum obtained from *Astragalus gummifer* Labillardière and other species of *Astragalus* grown in Western Asia; *see* Section 13.

The gum consists of a mixture of water-insoluble and water-soluble polysaccharides. Bassorin, which constitutes 60–70% of the gum, is the main water-insoluble portion, while the remainder of the gum consists of the water-soluble material tragacanthin. On hydrolysis, tragacanthin yields L-arabinose, L-fucose, D-xylose, D-galactose, and D-galacturonic acid. Tragacanth gum also contains small amounts of cellulose, starch, protein, and ash.

Tragacanth gum has an approximate molecular weight of 840 000.

5 Structural Formula

See Section 4.

6 Functional Category

Suspending agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Tragacanth gum is used as an emulsifying and suspending agent in a variety of pharmaceutical formulations. It is used in creams, gels, and emulsions at various concentrations according to the application of the formulation and the grade of gum used.

Tragacanth gum is also used similarly in cosmetics and food products, and has been used as a diluent in tablet formulations.

8 Description

Tragacanth gum occurs as flattened, lamellated, frequently curved fragments, or as straight or spirally twisted linear pieces from 0.5–2.5 mm in thickness; it may also be obtained in a powdered form. White to yellowish in color, tragacanth is a translucent, odorless substance, with an insipid mucilaginous taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for tragacanth.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Botanical characteristics	—	—	+
Microbial limits	—	+	+
Flow time	—	+	—
Lead	—	—	≤0.001%
Heavy metals	—	—	≤20 ppm
Methylcellulose	—	+	—
Acacia	—	+	—
Foreign matter	—	≤1.0%	—
Karaya gum	+	—	+
Sterculia gum	—	+	—
Organic volatile impurities	—	—	+
Ash	≤4.0%	≤4.0%	—

10 Typical Properties

Acidity/alkalinity: pH = 5–6 for a 1% w/v aqueous dispersion.
Acid value: 2–5
Moisture content: ≤15% w/w
Particle size distribution: for powdered grades 50% w/w passes through a 73.7 μm mesh.
Solubility: practically insoluble in water, ethanol (95%), and other organic solvents. Although insoluble in water, tragacanth gum swells rapidly in 10 times its own weight of either hot or cold water to produce viscous colloidal sols or semigels. *See also* Section 18.
Specific gravity: 1.250–1.385
Viscosity (dynamic): the viscosity of tragacanth dispersions varies according to the grade and source of the material. Typically, 1% w/v aqueous dispersions may range in viscosity from 100–4000 mPa s (100–4000 cP) at 20°C. Viscosity increases with increasing temperature and concentration, and decreases with increasing pH. Maximum initial viscosity occurs at pH 8, although the greatest stability of tragacanth dispersions occurs at about pH 5. *See also* Sections 11 and 12.

11 Stability and Storage Conditions

Both the flaked and powdered forms of tragacanth are stable. Tragacanth gels are liable to exhibit microbial contamination with enterobacterial species, and stock solutions should therefore contain suitable antimicrobial preservatives. In emulsions, glycerin or propylene glycol are used as preservatives; in gel formulations, tragacanth is usually preserved with either 0.1% w/v benzoic acid or sodium benzoate. A combination of 0.17%

w/v methylparaben and 0.03% w/v propylparaben is also an effective preservative for tragacanth gels;(1) *see also* Section 12. Gels may be sterilized by autoclaving. Sterilization by gamma irradiation causes a marked reduction in the viscosity of tragacanth dispersions.(2)

Tragacanth dispersions are most stable at pH 4–8, although stability is satisfactory at higher pH or as low as pH 2.

The bulk material should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

At pH 7, tragacanth has been reported to considerably reduce the efficacy of the antimicrobial preservatives benzalkonium chloride, chlorobutanol, and methylparaben, and to a lesser extent that of phenol and phenylmercuric acetate.(3) However, at $pH < 5$ tragacanth was reported to have no adverse effects on the preservative efficacy of benzoic acid, chlorobutanol, or methylparaben.(1)

The addition of strong mineral and organic acids can reduce the viscosity of tragacanth dispersions. Viscosity may also be reduced by the addition of alkali or sodium chloride, particularly if the dispersion is heated. Tragacanth is compatible with relatively high salt concentrations and most other natural and synthetic suspending agents such as acacia, carboxymethylcellulose, starch, and sucrose. A yellow colored, stringy, precipitate is formed with 10% w/v ferric chloride solution.

13 Method of Manufacture

Tragacanth gum is the air-dried gum obtained from *Astragalus gummifer* Labillardière and other species of *Astragalus* grown principally in Iran, Syria, and Turkey. A low-quality gum is obtained by collecting the natural air-dried exudate from *Astragalus* bushes. A higher-grade material is obtained by making incisions in the trunk and branches of the bush, which are held open with variously sized wooden pegs. The exudate is left to drain from the incision and dry naturally in the air before being collected. The size and position of the wooden wedges determine the physical form of the exudate, while the drying conditions determine the color of the gum. After collection, the tragacanth gum is sorted by hand into various grades, such as ribbons or flakes.

14 Safety

Tragacanth has been used for many years in oral pharmaceutical formulations and food products, and is generally regarded as an essentially nontoxic material. Tragacanth has been shown to be noncarcinogenic.(4) However, hypersensitivity reactions, which are occasionaly severe, have been reported following ingestion of products containing tragacanth.(5,6) Contact dermatitis has also been reported following the topical use of tragacanth formulations.(7)

The WHO has not specified an acceptable daily intake for tragacanth gum, as the daily intake necessary to achieve a desired effect, and its background levels in food, were not considered to be a hazard to health.(8)

LD_{50} (hamster, oral): 8.8 g/kg(9)
LD_{50} (mouse, oral): 10 g/kg
LD_{50} (rabbit, oral): 7.2 g/kg
LD_{50} (rat, oral): 16.4 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Tragacanth gum may be irritant to the skin and eyes. Eye protection, gloves, and a dust mask are recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (buccal/sublingual tablets, oral powders, suspensions, syrups, and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

See Section 18.

18 Comments

Tragacanth gum is a naturally occurring material whose physical properties vary greatly according to the grade and source of the material. Samples can contain relatively high levels of bacterial contamination.(10,11)

Hog gum (caramania gum), obtained from species of *Prunus*, and sterculia gum have been used in industrial applications as substitutes for tragacanth.

Powdered tragacanth gum tends to form lumps when added to water and aqueous dispersions should therefore be agitated vigorously with a high-speed mixer. However, aqueous dispersions are more readily prepared by first prewetting the tragacanth with a small quantity of a wetting agent such as ethanol (95%), glycerin, or propylene glycol. If lumps form, they usually disperse on standing. Dispersion is generally complete after 1 hour. If other powders, such as sucrose, are to be incorporated into a tragacanth formulation the powders are best mixed together in the dry state.

Some pharmacopeias, such as JP 2001, contain a specification for powdered tragacanth.

A specification for tragacanth is contained in the Food Chemicals Codex (FCC).

19 Specific References

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21 Authors

PJ Weller.

22 Date of Revision

13 April 2005.

Trehalose

1 Nonproprietary Names

None adopted.

2 Synonyms

*C*Ascend*; (α-D-glucosido)-α-D-glucoside; mycose; natural trehalose; α,α-trehalose; trehalose dihydrate.

3 Chemical Name and CAS Registry Number

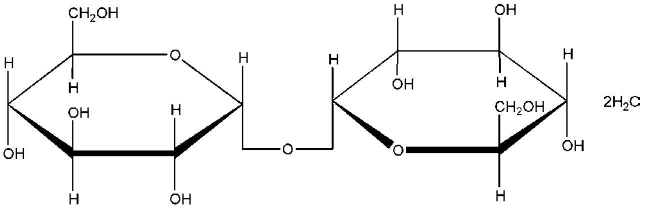
α-D-Glucopyranosyl-α-D-glucopyranoside anhydrous [99-20-7]
α-D-Glucopyranosyl-α-D-glucopyranoside dihydrate [6138-23-4]

See also Section 17.

4 Empirical Formula and Molecular Weight

$C_{12}H_{22}O_{11}$	342.31 (anhydrous)
$C_{12}H_{22}O_{11}\cdot 2H_2O$	378.33 (dihydrate)

5 Structural Formula



α,α-Trehalose dihydrate

6 Functional Category

Coloring adjuvant; flavor enhancer; freeze-drying excipient; humectant; stabilizing agent; sweetening agent; tablet diluent; thickening agent.

7 Applications in Pharmaceutical Formulation or Technology

Trehalose is used for the lyoprotection of therapeutic proteins, particularly for parenteral administration. Other pharmaceutically relevant applications include use as an excipient for diagnostic assay tablets;(1) for stabilization during the freeze–thaw and lyophilization of liposomes;(2) and for stabilization of blood cells,(3) cosmetics,(4) and monoclonal antibodies.(5) Trehalose may also be used in formulations for topical application.(6)

8 Description

Trehalose occurs as virtually odorless, white or almost white crystals with a sweet taste (approximately 45% of the sweetness of sucrose).

9 Pharmacopeial Specifications

—

10 Typical Properties

Acidity/alkalinity: pH = 4.5–6.5 (30% w/v aqueous solution)
Melting point: 97°C (for the dihydrate)
Moisture content: 9.5% (for the dihydrate)
Solubility: soluble in water; very slightly soluble in ethanol (95%); practically insoluble in ether.
Specific rotation $[\alpha]_D^{20}$**:** +179.7° (5% w/v aqueous solution)

See also Section 18.

11 Stability and Storage Conditions

Trehalose is a relatively stable material. At 60°C for 5 hours it loses not more than 1.5% w/w of water (the dihydrate water of crystallization is retained). Open stored powder may liquefy at high relative humidity ($\geqslant$90%).

Trehalose should be stored in a cool, dry place in a well-sealed container.

12 Incompatibilities

Trehalose is incompatible with strong oxidizing agents, especially in the presence of heat.

13 Method of Manufacture

Trehalose is prepared from liquefied starch by a multistep enzymatic process.(7) The commercial product is the dihydrate.

14 Safety

Trehalose is used in cosmetics, foods, and parenteral and nonparenteral pharmaceutical formulations. It is generally regarded as a relatively nontoxic and nonirritant material when used as an excipient.

In the gut, trehalose is rapidly metabolized to glucose by the specific enzyme trehalase. A small minority of the population exhibits a primary (hereditary) or secondary (acquired) trehalase deficiency and thus may experience intestinal discomfort after ingestion of excessive amounts of trehalose owing to the osmotic activity of undigested trehalose in the gut. However, smaller amounts of trehalose are tolerated by such individuals without any symptoms.(7)

Trehalose is reported to have substantially less cariogenic potential than sucrose.

LD_{50} (dog, IV): >1 g/kg
LD_{50} (dog, oral): >5 g/kg
LD_{50} (mouse, IV): >1 g/kg
LD_{50} (mouse, oral): >5 g/kg
LD_{50} (rat, IV): >1 g/kg
LD_{50} (rat, oral): >5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16 Regulatory Status

GRAS listed. In the UK trehalose may be used in certain food applications. Included in parenteral and nonparenteral investigational formulations.

17 Related Substances

Isotrehalose; neotrehalose.

Isotrehalose

CAS number: [499-23-0]
Synonyms: β,β-trehalose.

Neotrehalose

CAS number: [585-91-1]
Synonyms: α,β-trehalose.

18 Comments

α,α-Trehalose is the only naturally occurring isomer of trehalose and occurs as the dihydrate. However, α,β-trehalose (neotrehalose) and β,β-trehalose (isotrehalose) have been synthesized and are also available commercially. *See also* Section 17.

Trehalose is a nonreducing sugar and therefore does not react with amino acids or proteins as a part of Maillard browning. It is relatively stable under low-pH conditions compared to other disaccharides.

It should be noted that although trehalose dihydrate is quoted to have a melting point of 97°C, the true nature of this melting process has been the subject of debate in the literature,(8–10) including the transformation of the dihydrate into the anhydrous form. Anhydrous crystalline trehalose has been reported to melt at 203°C,(11) although higher values (215°C) have also been quoted in the literature.(12)

The glass transition temperature of trehalose is reported to be approximately 120°C (anhydrous amorphous phase).(13)

The EINECS number for trehalose is 202-739-6.

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21 Authors

OS McGarvey, DQM Craig, VL Kett.

22 Date of Revision

7 August 2005.

Triacetin

1 Nonproprietary Names

BP: Triacetin
PhEur: Glycerolum triacetas
USP: Triacetin

2 Synonyms

Captex 500; E1518; glycerol triacetate; glyceryl triacetate; triacetyl glycerine.

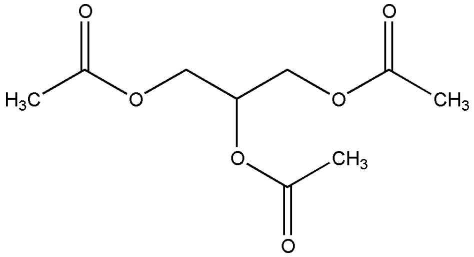
3 Chemical Name and CAS Registry Number

1,2,3-Propanetriol triacetate [102-76-1]

4 Empirical Formula and Molecular Weight

$C_9H_{14}O_6$ 218.21

5 Structural Formula



6 Functional Category

Humectant; plasticizer; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Triacetin is mainly used as a hydrophilic plasticizer in both aqueous and solvent-based polymeric coating of capsules, tablets, beads, and granules; typical concentrations used are 10–35% w/w.(1,2)

Triacetin is used in cosmetics, perfumery, and foods as a solvent and as a fixative in the formulation of perfumes and flavors.

8 Description

Triacetin is a colorless, viscous liquid with a slightly fatty odor.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for triacetin.

Test	PhEur 2005	USP 28
Appearance	+	—
Characters	+	—
Identification	+	+
Specific gravity	1.159–1.164	1.152–1.158
Refractive index	1.429–1.432	1.429–1.430
Acidity	+	+
Water	⩽0.2%	⩽0.2%
Assay (anhydrous basis)	97.0–100.5%	97.0–100.5%

10 Typical Properties

Autoignition temperature: 432°C
Boiling point: 258°C
Density: 1.16 g/cm^3 at 25°C
Explosive limits:
1.05% at 189°C lower limit;
7.73% at 215°C upper limit.
Flash point: 153°C (open cup)
Freezing point: 3.2°C (supercools to about –70°C)
Melting point: −78°C
Refractive index: n_D^{25} = 1.4296
Solubility: *see* Table II.

Table II: Solubility of triacetin.

Solvent	Solubility at 20°C
Carbon disulfide	Miscible
Chloroform	Miscible
Ethanol	Miscible
Ethanol (95%)	Miscible
Ether	Miscible
Toluene	Miscible
Water	1 in 14

Vapor density (relative): 7.52 (air = 1)
Vapor pressure: 133 Pa (1 mmHg) at 100°C
Viscosity (dynamic):
1111 mPa s (1111 cP) at –17.8°C;
107 mPa s (107 cP) at 0°C;
17.4 mPa s (17.4 cP) at 25°C;
1.8 mPa s (1.8 cP) at 100°C.

11 Stability and Storage Conditions

Triacetin is stable and should be stored in a well-closed, nonmetallic container, in a cool, dry place.

12 Incompatibilities

Triacetin is incompatible with metals and may react with oxidizing agents. Triacetin may destroy rayon fabric.

13 Method of Manufacture

Triacetin is prepared by the esterification of glycerin with acetic anhydride.

14 Safety

Triacetin is used in oral pharmaceutical formulations and is generally regarded as a relatively nontoxic and nonirritant material at the levels employed as an excipient.(3)

LD_{50} (dog, IV): 1.5 g/kg(4)
LD_{50} (mouse, IP): 1.4 g/kg
LD_{50} (mouse, IV): 1.6 g/kg
LD_{50} (mouse, oral): 1.1 g/kg
LD_{50} (mouse, SC): 2.3 g/kg
LD_{50} (rabbit, IV): 0.75 g/kg
LD_{50} (rat, IP): 2.1 g/kg
LD_{50} (rat, oral): 3 g/kg
LD_{50} (rat, SC): 2.8 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Triacetin may be irritant to the eyes; eye protection and gloves are recommended.

16 Regulatory Status

GRAS listed. Accepted in Europe as a food additive in certain applications. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets and gels). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

—

18 Comments

A specification for triacetin is contained in the Food Chemicals Codex (FCC). The EINECS number for triacetin is 203-051-9.

19 Specific References

1 Shah PS, Zatz JL. Plasticization of cellulose esters used in the coating of sustained release solid dosage forms. *Drug Dev Ind Pharm* 1992; **18**: 1759–1772.
2 Williams RO, Wheatley TA, Liu J. Influence of plasticization and curing conditions on the mechanical properties of aqueous based cellulose acetate films. *STP Pharma Sci* 1999; **9**(6): 545–553.
3 Fiume MZ. Final report on the safety assessment of triacetin. *Int J Toxicol* 2003; **22**(Suppl 2): 1–10.
4 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 3503.

20 General References

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Johnson K, Hathaway R, Leung P, Franz R. Effect of triacetin and polyethylene glycol 400 on some physical properties of hydroxypropyl methylcellulose free films. *Int J Pharm* 1991; **73**: 197–208.
Lehmann KOR. Chemistry and application properties of polymethacrylate coating systems. In: McGinity JW, ed. *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*. New York: Marcel Dekker, 1989: 224.
Lin S-Y, Lee C-J, Lin Y-Y. The effect of plasticizers on compatibility, mechanical properties, and adhesion strength of drug-free Eudragit E films. *Pharm Res* 1991; **8**: 1137–1143.
Rowe RC. Materials used in the film coating of oral dosage forms. In: Florence AT, ed. *Critical Reports on Applied Chemistry,* vol. 6. Oxford: Blackwell Scientific, 1984: 1–36.

21 Authors

A Palmieri.

22 Date of Revision

13 April 2005.

Tributyl Citrate

1 Nonproprietary Names

USPNF: Tributyl citrate

2 Synonyms

Citric acid, tributyl ester; *Citroflex 4*; TBC; tri-*n*-butyl citrate; tributyl 2-hydroxy-1,2,3-propanetricarboxylate.

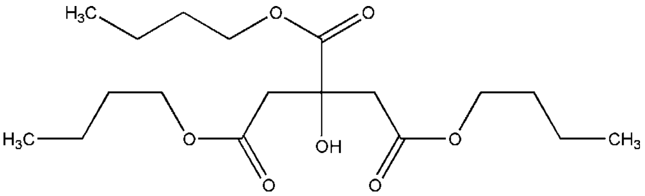
3 Chemical Name and CAS Registry Number

1,2,3-Propanetricarboxylic acid, 2-hydroxy, tributyl ester [77-94-1]

4 Empirical Formula and Molecular Weight

$C_{18}H_{32}O_7$ 360.5

5 Structural Formula



6 Functional Category

Plasticizer.

7 Applications in Pharmaceutical Formulation or Technology

Tributyl citrate is used to plasticize polymers in formulated pharmaceutical coatings. The coating applications include capsules, tablets, beads, and granules for taste masking, immediate release, sustained-release, and enteric formulations.(1–6)

8 Description

Tributyl citrate is a clear, odorless, practically colorless, oily liquid.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for tributyl citrate.

Test	USPNF 23
Identification	+
Specific gravity	1.037–1.045
Refractive index	1.443–1.445
Acidity	+
Water	$\leqslant$0.2%
Heavy metals	$\leqslant$0.001%
Assay (anhydrous basis)	$\geqslant$99.0%

10 Typical Properties

Acid value: 0.02
Boiling point: 322°C (decomposes)
Flash point: 185°C
Pour point: −62°C
Solubility: miscible with acetone, ethanol, and vegetable oil; practically insoluble in water.
Viscosity: 32 mPa s (32 cP) at 25°C

11 Stability and Storage Conditions

Tributyl citrate should be stored in well-closed containers in a cool, dry location at temperatures not exceeding 38°C. When stored in accordance with these conditions, tributyl citrate is a stable material.

12 Incompatibilities

Tributyl citrate is incompatible with strong alkalis and oxidizing materials.

13 Method of Manufacture

Tributyl citrate is prepared by the esterification of citric acid with butanol.

14 Safety

Tributyl citrate is used in oral pharmaceutical formulations. It is generally regarded as an essentially nontoxic and nonirritating material. However, ingestion of large quantities may be harmful.

LD_{50} (cat, oral): >50 mL/kg(7)
LD_{50} (mouse, IP): 2.9 g/kg
LD_{50} (rat, oral): >30 mL/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Tributyl citrate may be irritating to the eyes. It may also be irritating to the respiratory system at elevated temperatures.

Gloves and eye protection are recommended for normal handling, and a respirator is recommended for elevated temperatures.

16 Regulatory Status

Approved in the US for indirect food contact in food films. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Acetyltributyl citrate; acetyltriethyl citrate; triethyl citrate.

18 Comments

The EINECS number for tributyl citrate is 201-071-2.

19 Specific References

1 Gutierrez-Rocca JC, McGinity JW. Influence of water soluble and insoluble plasticizer on the physical and mechanical properties of acrylic resin copolymers. *Int J Pharm* 1994; **103**: 293–301.

2 Lehmann K. Chemistry and application properties of polymethacrylate coating systems. In: McGinity JW, ed. *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*. New York: Marcel Dekker, 1989: 153–245.

3 Steurnagel CR. Latex emulsions for controlled drug delivery. In: McGinity JW, ed. *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*. New York: Marcel Dekker, 1989: 1–61.

4 Gutierrez-Rocca JC, McGinity JW. Influence of aging on the physical-mechanical properties of acrylic resin films cast from aqueous dispersions and organic solutions. *Drug Dev Ind Pharm* 1993; **19**(3): 315–332.

5 Felton LA, McGinity JW. Influence of plasticisers on the adhesive properties of an acrylic resin copolymer to hydrophilic and hydrophobic tablet compacts. *Int J Pharm* 1997; **154**(2): 167–178.

6 Okarter TU, Singla K. The effects of plasticisers on the release of metoprolol tartrate from granules coated with a polymethacrylate film. *Drug Dev Ind Pharm* 2000; **26**(3): 323–329.

7 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials,* 11th edn. New York: Wiley, 2004: 3513.

20 General References

Morflex Inc. Technical literature: *Citrate esters*, 2000.

21 Authors

SW Kennedy.

22 Date of Revision

13 August 2005.

Triethanolamine

1 Nonproprietary Names

BP: Triethanolamine
PhEur: Trolaminum
USPNF: Trolamine

2 Synonyms

TEA; *Tealan*; triethylolamine; trihydroxytriethylamine; tris (hydroxyethyl)amine.

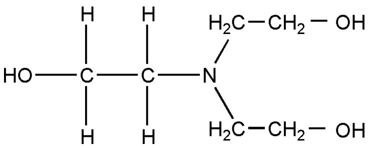
3 Chemical Names and CAS Registry Number

2,2′,2″-Nitrilotriethanol [102-71-6]

4 Empirical Formula and Molecular Weight

$C_6H_{15}NO_3$ 149.19

5 Structural Formula



6 Functional Category

Alkalizing agent; emulsifying agent.

7 Applications in Pharmaceutical Formulation or Technology

Triethanolamine is widely used in topical pharmaceutical formulations primarily in the formation of emulsions.

When mixed in equimolar proportions with a fatty acid, such as stearic acid or oleic acid, triethanolamine forms an anionic soap with a pH of about 8, which may be used as an emulsifying agent to produce fine-grained, stable oil-in-water emulsions. Concentrations that are typically used for emulsification are 2–4% v/v of triethanolamine and 2–5 times that of fatty acids. In the case of mineral oils, 5% v/v of triethanolamine will be needed, with an appropriate increase in the amount of fatty acid used. Preparations that contain triethanolamine soaps tend to darken on storage. However, discoloration may be reduced by avoiding exposure to light and contact with metals and metal ions.

Triethanolamine is also used in salt formation for injectable solutions and in topical analgesic preparations. It is also used in sun-screen preparations.(1)

Triethanolamine is used as an intermediate in the manufacturing of surfactants, textile specialties, waxes, polishes, herbicides, petroleum demulsifiers, toilet goods, cement additives, and cutting oils. Triethanolamine is also claimed to be used for the production of lubricants for the rubber gloves and textile industries. Other general uses are as buffers, solvents, and polymer plasticizers, and as a humectant.

See also Section 18.

8 Description

Triethanolamine is a clear, colorless to pale yellow-colored viscous liquid having a slight ammoniacal odor. It is a mixture of bases, mainly 2,2′,2″-nitrilotriethanol although it also contains 2,2′-iminobisethanol (diethanolamine) and smaller amounts of 2-aminoethanol (monoethanolamine).

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for triethanolamine.

Test	PhEur 2005	USPNF 23
Characters	+	—
Identification	+	+
Appearance of solution	+	—
Related substances	+	—
Heavy metals	⩽10 ppm	—
Water	⩽1.0%	⩽0.5%
Sulfated ash	⩽0.1%	⩽0.05%
Impurities	+	—
Organic volatile impurities	—	+
Specific gravity	—	1.120–1.128
Refractive index	—	1.481–1.486
Assay	99.0–103.0%	99.0–107.4%

10 Typical Properties

Acidity/alkalinity: pH = 10.5 (0.1 N solution)
Boiling point: 335°C
Flash point: 208°C
Freezing point: 21.6°C
Hygroscopicity: very hygroscopic.
Melting point: 20–21°C
Moisture content: 0.09%
Solubility: *see* Table II.

Table II: Solubility of triethanolamine.

Solvent	Solubility at 20°C
Acetone	Miscible
Benzene	1 in 24
Carbon tetrachloride	Miscible
Ethyl ether	1 in 63
Methanol	Miscible
Water	Miscible

Surface tension: 48.9 mN/m (48.9 dynes/cm) at 25°C
Viscosity (dynamic): 590 mPa s (590 cP) at 30°C

11 Stability and Storage Conditions

Triethanolamine may turn brown on exposure to air and light.

The 85% grade of triethanolamine tends to stratify below 15°C; homegeneity can be restored by warming and mixing before use.

Triethanolamine should be stored in an airtight container protected from light, in a cool, dry place.

See Monoethanolamine for further information.

12 Incompatibilities

Triethanolamine is a tertiary amine that contains hydroxy groups; it is capable of undergoing reactions typical of tertiary amines and alcohols. Triethanolamine will react with mineral acids to form crystalline salts and esters. With the higher fatty acids, triethanolamine forms salts that are soluble in water and have characteristics of soaps. Triethanolamine will also react with copper to form complex salts. Discoloration and precipitation can take place in the presence of heavy metal salts.

Triethanolamine can react with reagents such as thionyl chloride to replace the hydroxy groups with halogens. The products of these reactions are very toxic, resembling other nitrogen mustards.

13 Method of Manufacture

Triethanolamine is prepared commercially by the ammonolysis of ethylene oxide. The reaction yields a mixture of monoethanolamine, diethanolamine, and triethanolamine, which are separated to obtain the pure products.

14 Safety

Triethanolamine is used primarily as an emulsifying agent in a variety of topical pharmaceutical preparations. Although generally regarded as a nontoxic material,(2) triethanolamine may cause hypersensitivity or be irritant to the skin when present in formulated products. The lethal human oral dose of triethanolamine is estimated to be 5–15 g/kg body-weight.

Following concern about the possible production of nitrosamines in the stomach, the Swiss authorities have restricted the use of triethanolamine to preparations intended for external use.(3)

LD_{50} (guinea pig, oral): 5.3 g/kg(4)
LD_{50} (mouse, IP): 1.45 g/kg
LD_{50} (mouse, oral): 7.4 g/kg
LD_{50} (rat, oral): 8 g/kg

15 Handling Precautions

Triethanolamine may be irritant to the skin, eyes, and mucous membranes. Inhalation of vapor may be harmful. Protective clothing, gloves, eye protection, and a respirator are recommended. Ideally, triethanolamine should be handled in a fume cupboard. On heating, triethanolamine forms highly toxic nitrous fumes. Triethanolamine is combustible.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Diethanolamine; monoethanolamine.

18 Comments

Various grades of triethanolamine are available. The standard commercial grade contains 85% triethanolamine. The superior grade contains 98–99% triethanolamine.

One volume part of triethanolamine with 5–7 parts of a mixture of CaO_2 and ZnO_2 is used as a filling material that enhances the restorative process in periodontal tissues. Triethanolamine is recommended as the preferred stabilizer to be used in latex polymerization because of its weak mutagenic effect in the Ames tests.

The EINECS number for triethanolamine is 203-049-8.

19 Specific References

1 Turkoglu M, Yener S. Design and *in vivo* evaluation of ultrafine inorganic-oxide-containing-sunscreen formulations. *Int J Cosmet Sci* 1997; **19**(4): 193–201.
2 Maekawa A, Onodera H, Tanigawa H, *et al*. Lack of carcinogenicity of triethanolamine in F344 rats. *J Toxicol Environ Health* 1986; **19**(3): 345–357.
3 Anonymous. Trolamine: concerns regarding potential carcinogenicity. *WHO Drug Inf* 1991; **5**: 9.
4 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 3568.

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Friberg SE, Wohn CS, Lockwood FE. The influence of solvent on nonaqueous lyotropic liquid crystalline phase formed by triethanolamine oleate. *J Pharm Sci* 1985; **74**(7): 771–773.

Ramsay B, Lawrence CM, Bruce JM, Shuster S. The effect of triethanolamine application on anthralin-induced inflammation and therapeutic effect in psoriasis. *J Am Acad Dermatol* 1990; **23**: 73–76.

Yano H, Noda A, Hukuhara T, Miyazawa K. Generation of maillard-type compounds from triethanolamine alone. *J Am Oil Chem Soc* 1997; **74**(7): 891–893.

21 Authors

SR Goskonda, JC Lee.

22 Date of Revision

13 April 2005.

Triethyl Citrate

1 Nonproprietary Names

BP: Triethyl citrate
PhEur: Triethylis citras
USPNF: Triethyl citrate

2 Synonyms

Citric acid, ethyl ester; *Citroflex 2*; *Citrofol AI*; E1505; *Hydagen CAT*; TEC.

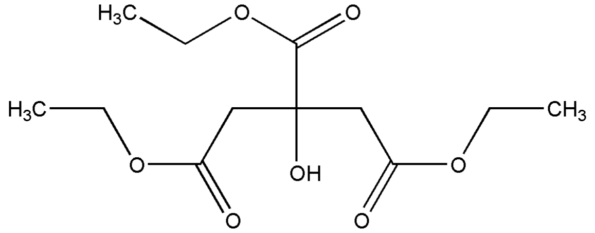
3 Chemical Name and CAS Registry Number

2-Hydroxy-1,2,3-propanetricarboxylic acid, triethyl ester [77-93-0]

4 Empirical Formula and Molecular Weight

$C_{12}H_{20}O_7$ 276.29

5 Structural Formula



6 Functional Category

Plasticizer.

7 Applications in Pharmaceutical Formulation or Technology

Triethyl citrate and the related esters acetyltriethyl citrate, tributyl citrate, and acetyltributyl are used to plasticize polymers in formulated pharmaceutical coatings.(1–5) The coating applications include capsules, tablets, beads, and granules for taste masking, immediate release, sustained-release, and enteric formulations.

Triethyl citrate is also used as a direct food additive for flavoring, for solvency, and as a surface active agent.

8 Description

Triethyl citrate is a clear, odorless, practically colorless, oily liquid.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for triethyl citrate.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Appearance	+	—
Specific gravity	—	1.135–1.139
Refractive index	1.440–1.446	1.439–1.441
Acidity	+	+
Related substances	+	—
Sulfated ash	⩽0.1%	—
Heavy metals	⩽5 ppm	⩽0.001%
Water	⩽0.25%	⩽0.25%
Assay (anhydrous basis)	98.5–101.0%	99.0–100.5%

10 Typical Properties

Acid value: 0.02
Boiling point: 288°C (decomposes)
Flash point: 155°C
Pour point: −45°C
Solubility: soluble 1 in 125 of peanut oil, 1 in 15 of water. Miscible with ethanol (95%), acetone, and propan-2-ol.
Viscosity (dynamic): 35.2 mPa s (35.2 cP) at 25°C

11 Stability and Storage Conditions

Triethyl citrate should be stored in a closed container in a cool, dry location. When stored in accordance with these conditions, triethyl citrate is a stable product.

12 Incompatibilities

Triethyl citrate is incompatible with strong alkalis and oxidizing materials.

13 Method of Manufacture

Triethyl citrate is prepared by the esterification of citric acid and ethanol in the presence of a catalyst.

14 Safety

Triethyl citrate is used in oral pharmaceutical formulations and as a direct food additive. It is generally regarded as a nontoxic and nonirritant material. However, ingestion of large quantities may be harmful.

LD_{50} (mouse, IP): 1.75 g/kg(6)
LD_{50} (rat, IP): 4 g/kg
LD_{50} (rat, oral): 5.9 g/kg
LD_{50} (rat, SC): 6.6 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Triethyl citrate is irritating to the eyes and may irritate the skin. Irritating to the respiratory system as a mist or at elevated temperatures. Gloves, eye protection, and a respirator are recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Acetyltributyl citrate; acetyltriethyl citrate; tributyl citrate.

18 Comments

A specification for triethyl citrate is contained in the Food Chemicals Codex (FCC). The EINECS number for triethyl citrate is 201-070-7.

19 Specific References

1 Gutierrez-Rocca JC, McGinity JW. Influence of water soluble and insoluble plasticizers on the physical and mechanical properties of acrylic resin copolymers. *Int J Pharm* 1994; **103**: 293–301.

2 Lehmann K. Chemistry and application properties of polymethacrylate coating systems. In: McGinity JW, ed. *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*. New York: Marcel Dekker, 1989: 153–245.

3 Steurnagel CR. Latex emulsions for controlled drug delivery. In: McGinity JW, ed. *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*. New York: Marcel Dekker, 1989: 1–61.

4 Gutierrez-Rocca JC, McGinity JW. Influence of aging on the physical–mechanical properties of acrylic resin films cast from aqueous dispersions and organic solutions. *Drug Dev Ind Pharm* 1993; **19**(3): 315–332.

5 Liu J, Williams R. Properties of heat-humidity cured cellulose acetate phthalate free films. *Eur J Pharm Sci* 2002; **17**(1–2): 31–41.

6 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 3546.

20 General References

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21 Authors

SW Kennedy.

22 Date of Revision

13 August 2005.

Vanillin

1 Nonproprietary Names

BP: Vanillin
PhEur: Vanillinum
USPNF: Vanillin

2 Synonyms

4-Hydroxy-*m*-anisaldehyde; *p*-hydroxy-*m*-methoxybenzaldehyde; 3-methoxy-4-hydroxybenzaldehyde; methylprotocatechuic aldehyde; *Rhovanil*; vanillic aldehyde.

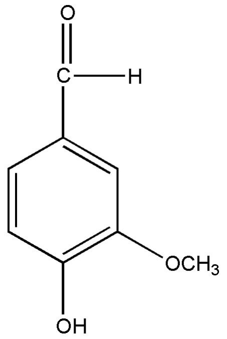
3 Chemical Name and CAS Registry Number

4-Hydroxy-3-methoxybenzaldehyde [121-33-5]

4 Empirical Formula and Molecular Weight

$C_8H_8O_3$ 152.15

5 Structural Formula



6 Functional Category

Flavoring agent.

7 Applications in Pharmaceutical Formulation or Technology

Vanillin is widely used as a flavor in pharmaceuticals, foods, beverages, and confectionery products, to which it imparts a characteristic taste and odor of natural vanilla. It is also used in perfumes, as an analytical reagent and as an intermediate in the synthesis of a number of pharmaceuticals, particularly methyldopa. Additionally, it has been investigated as a potential therapeutic agent in sickle cell anemia(1) and is claimed to have some antifungal properties.(2)

In food applications, vanillin has been investigated as a preservative.(3,4)

As a pharmaceutical excipient, vanillin is used in tablets, solutions (0.01–0.02% w/v), syrups, and powders to mask the unpleasant taste and odor characteristics of certain formulations, such as caffeine tablets and polythiazide tablets. It is similarly used in film coatings to mask the taste and odor of vitamin tablets.

Vanillin has also been investigated as a photostabilizer in furosemide 1% w/v injection, haloperidol 0.5% w/v injection, and thiothixene 0.2% w/v injection.(5)

8 Description

White or cream, crystalline needles or powder with characteristic vanilla odor and sweet taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for vanillin.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Melting range	81–84°C	81–83°C
Loss on drying	⩽1.0%	⩽1.0%
Sulfated ash	⩽0.05%	—
Residue on ignition	—	⩽0.05%
Related substances	+	—
Reaction with sulfuric acid	+	—
Organic volatile impurities	—	+
Assay (dried basis)	99.0–101.0%	97.0–103.0%

10 Typical Properties

Acidity/alkalinity: aqueous solutions are acid to litmus.
Boiling point: 284–285°C (with decomposition)
Density (bulk): 0.6 g/cm^3
Flash point: 153°C (closed cup)
Melting point: 81–83°C
Solubility: *see* Table II.
Specific gravity: 1.056 (liquid)

Table II: Solubility of vanillin.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	Soluble
Alkali hydroxide solutions	Soluble
Chloroform	Soluble
Ethanol (95%)	1 in 2
Ethanol (70%)	1 in 3
Ether	Soluble
Glycerin	1 in 20
Methanol	Soluble
Oils	Soluble
Water	1 in 100 1 in 16 at 80°C

11 Stability and Storage Conditions

Vanillin oxidizes slowly in moist air and is affected by light.

Solutions of vanillin in ethanol decompose rapidly in light to give a yellow-colored, slightly bitter tasting solution of 6,6′-dihydroxy-5,5′-dimethoxy-1,1′-biphenyl-3,3′-dicarbaldehyde. Alkaline solutions also decompose rapidly to give a brown-colored solution. However, solutions stable for several months may be produced by adding sodium metabisulfite 0.2% w/v as an antioxidant.(6)

The bulk material should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

Incompatible with acetone, forming a brightly colored compound.(7) A compound practically insoluble in ethanol is formed with glycerin.

13 Method of Manufacture

Vanillin occurs naturally in many essential oils and particularly in the pods of *Vanilla planifolia* and *Vanilla tahitensis*. Industrially, vanillin is prepared from lignin, which is obtained from the sulfite wastes produced during paper manufacture. Lignin is treated with alkali at elevated temperature and pressure, in the presence of a catalyst, to form a complex mixture of products from which vanillin is isolated. Vanillin is then purified by successive recrystallizations.

Vanillin may also be prepared synthetically by condensation, in weak alkali, of a slight excess of guaiacol with glyoxylic acid at room temperature. The resultant alkaline solution, containing 4-hydroxy-3-methoxymandelic acid is oxidized in air, in the presence of a catalyst, and vanillin is obtained by acidification and simultaneous decarboxylation. Vanillin is then purified by successive recrystallizations.

14 Safety

There have been few reports of adverse reactions to vanillin, although it has been speculated that cross-sensitization with other structurally similar molecules, such as benzoic acid, may occur.(8) Adverse reactions that have been reported include contact dermatitis(9) and bronchospasm caused by hypersensitivity.(10)

The WHO has allocated an estimated acceptable daily intake for vanillin of up to 10 mg/kg body-weight.(11)

LD_{50} (guinea pig, IP): 1.19 g/kg(12)
LD_{50} (guinea pig, oral): 1.4 g/kg
LD_{50} (mouse, IP): 0.48 g/kg
LD_{50} (rat, IP): 1.16 g/kg
LD_{50} (rat, oral): 1.58 g/kg
LD_{50} (rat, SC): 1.5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the quantity of material handled. Eye protection is recommended. Heavy airborne concentrations of dust may present an explosion hazard.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral solutions, suspensions, syrups, and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Ethyl vanillin.

18 Comments

One part of synthetic vanillin is equivalent to 400 parts of vanilla pods. The EINECS number for vanillin is 204-465-2.

19 Specific References

1 Abraham DJ, Mehanna AS, Wireko FC, *et al.* Vanillin, a potential agent for the treatment of sickle cell anemia. *Blood* 1991; **77**: 1334–1341.
2 Lisá M, Leifertová I, Baloun J. A contribution to the antifungal effect of propolis [in German]. *Folia Pharm* 1989; **13**(1): 29–44.
3 Fitzgerald DJ, Stratford M, Narbad A. Analysis of the inhibition of food spoilage yeasts by vanillin. *Int J Food Microbiol* 2003; **86**(1–2): 113–122.
4 Fitzgerald DJ, Stratford M, Gasson MJ, Narbad A. The potential application of vanillin in preventing yeast spoilage of soft drinks and fruit juices. *J Food Prot* 2004; **67**(2): 391–395.
5 Thoma K, Klimek R. Photostabilization of drugs in dosage forms without protection from packaging materials. *Int J Pharm* 1991; **67**: 169–175.
6 Jethwa SA, Stanford JB, Sugden JK. Light stability of vanillin solutions in ethanol. *Drug Dev Ind Pharm* 1979; **5**: 79–85.
7 Thakur AB, Dayal S. Schiff base formation with nitrogen of a sulfonamido group. *J Pharm Sci* 1982; **71**: 1422.
8 Weiner M, Bernstein IL. *Adverse Reactions to Drug Formulation Agents: A Handbook of Excipients*. New York: Marcel Dekker, 1989: 238–239.
9 Wang X-S, Xue Y-S, Jiang Y, *et al.* Occupational contact dermatitis in manufacture of vanillin. *Chin Med J* 1987; **100**: 250–254.
10 Van Assendelft AHW. Bronchospasm induced by vanillin and lactose. *Eur J Respir Dis* 1984; **65**: 468–472.
11 FAO/WHO. Specifications for the identity and purity of food additives and their toxicological evaluation: some flavouring substances and non-nutritive sweetening agents. Eleventh report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1968; No. 383.
12 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials,* 11th edn. New York: Wiley, 2004: 3661–3662.

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22 Date of Revision

18 August 2005.

Vegetable Oil, Hydrogenated

1 Nonproprietary Names

BP: Hydrogenated vegetable oil
JP: Hydrogenated oil
USPNF: Hydrogenated vegetable oil
See also Sections 8,9, and 17.

2 Synonyms

Some trade names for materials derived from stated vegetable oils are shown below:

Hydrogenated cottonseed oil: *Akofine*; *Lubritab*; *Sterotex*.
Hydrogenated palm oil: *Softisan 154*.
Hydrogenated soybean oil: *Lipovol HS-K*; *Sterotex HM*.

3 Chemical Name and CAS Registry Number

Hydrogenated vegetable oil [68334-00-9]
Hydrogenated soybean oil [8016-70-4]

4 Empirical Formula and Molecular Weight

The USPNF 23 defines two types of hydrogenated vegetable oil, type I and type II, which differ in their physical properties and applications; *see* Sections 9 and 17.

5 Structural Formula

$R^1COOCH_2—CH(OOCR^2)—CH_2OOCR^3$

where R^1, R^2, and R^3 are mainly C_{15} and C_{17}.

6 Functional Category

Tablet and capsule lubricant; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Hydrogenated vegetable oil type I is used as a lubricant in tablet and capsule formulations.(1,2) It is used at concentrations of 1–6% w/w, usually in combination with talc. It may also be used as an auxiliary binder in tablet formulations.

Hydrogenated vegetable oil type I is additionally used as the matrix-forming material in lipophilic-based controlled-release formulations;(3–6) it may also be used as a coating aid in controlled-release formulations.

Other uses of hydrogenated vegetable oil type I include use as a viscosity modifier in the preparation of oil-based liquid and semisolid formulations; in the preparation of suppositories, to reduce the sedimentation of suspended components and to improve the solidification process; and in the formulation of liquid and semisolid fills for hard gelatin capsules.(7)

Fully hydrogenated vegetable oil products may also be used as alternatives to hard waxes in cosmetics and topical pharmaceutical formulations.

See also Section 17.

8 Description

Hydrogenated vegetable oil is a mixture of triglycerides of fatty acids. The two types that are defined in the USPNF 23 are characterized by their physical properties; *see* Section 9.

Hydrogenated vegetable oil type I occurs in various forms, e.g. fine powder, flakes, or pellets. The color of the material depends on the manufacturing process and the form. In general, the material is white to yellowish-white with the powder grades appearing more white-colored than the coarser grades.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for hydrogenated vegetable oil.

Test	BP 2004	JP 2001	USPNF 23	
			Type I	Type II
Identification	+	—	—	—
Characters	+	+	—	—
Melting range	57–70°C	—	57–85°C	20–50°C
Heavy metals	⩽10 ppm	+	⩽0.001%	⩽0.001%
Moisture and coloration	—	+	—	—
Alkali	—	+	—	—
Chloride	—	+	—	—
Nickel	—	+	—	—
Iodine value	⩽5	—	0–5	55–80
Saponification value	175–205	—	175–200	175–200
Loss on drying	⩽0.1%	—	⩽0.1%	⩽0.1%
Acid value	⩽4.0	⩽2.0	⩽4.0	⩽4.0
Unsaponifiable matter	⩽0.8%	—	⩽0.8%	⩽0.8%
Residue on ignition	—	⩽0.1%	—	—
Organic volatile impurities	—	—	+	+

10 Typical Properties

Density (tapped): 0.57 g/cm^3 for *Lubritab*
Melting point: 61–66°C for *Lubritab*
Particle size distribution: 85% $<$ 177 μm, 25% $<$ 74 μm in size for *Lubritab*. Average particle size is 104 μm.
Solubility: soluble in chloroform, petroleum spirit, and hot propan-2-ol; practically insoluble in water.

11 Stability and Storage Conditions

Hydrogenated vegetable oil type I is a stable material; typically it is assigned a 2-year shelf-life.

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatible with strong oxidizing agents.

13 Method of Manufacture

Hydrogenated vegetable oil type I is prepared from refined vegetable oils, which are hydrogenated using a catalyst.

14 Safety

Hydrogenated vegetable oil type I is used in food products and oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant excipient.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Gloves, eye protection, and a dust mask are recommended when handling fine powder grades.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets; rectal and vaginal suppositories and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Castor oil, hydrogenated; hydrogenated vegetable oil, type II; medium-chain triglycerides; suppository bases.

Hydrogenated vegetable oil, type II

Comments: hydrogenated vegetable oil type II includes partially hydrogenated vegetable oils from different sources that have a wide range of applications. In general, type II materials have lower melting ranges and higher iodine values than type I materials. Many type II materials are prepared to meet specific customer requirements for use in cosmetics. Type II materials may also be used in the manufacture of suppositories. *See also* Section 9.

18 Comments

Products from different manufacturers may vary owing to differences in the source of the vegetable oil used for hydrogenation. Certain materials are made from mixed hydrogenated oils, e.g. hydrogenated soybean oil and hydrogenated castor oil (*Sterotex K*).

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22 Date of Revision

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Water

1 Nonproprietary Names

BP: Purified water
JP: Purified water
PhEur: Aqua purificata
USP: Purified water
See also Sections 8 and 17.

2 Synonyms

Aqua; hydrogen oxide.

3 Chemical Name and CAS Registry Number

Water [7732-18-5]

4 Empirical Formula and Molecular Weight

H_2O 18.02

5 Structural Formula

H_2O

6 Functional Category

Solvent.

7 Applications in Pharmaceutical Formulation or Technology

Water is the most widely used excipient in pharmaceutical production operations. Specific grades of water are used for particular applications in concentrations up to 100%; *see* Table I. Purified water and water for injection are also used for cleaning operations during production of pharmaceutical products.

8 Description

The term 'water' is used to describe potable water that is freshly drawn direct from the public supply and is suitable for drinking. The chemical composition of potable water is variable and the nature and concentrations of the impurities in it depend upon the source from which it is drawn. Although potable water must be both palatable and safe to drink, for most pharmaceutical applications potable water is purified by distillation, ion exchange treatment, reverse osmosis, or some other suitable process to produce 'purified water'. For certain applications, water with pharmacopeial specifications differing from those of purified water should be used, e.g. water for injection; *see* Sections 9 and 18.

Water is a clear, colorless, odorless, and tasteless liquid.

Table I: Typical applications of specific grades of water.

Type	Use
Bacteriostatic water for injection	Diluent for ophthalmic and multiple-dose injections.
Potable water	Public supply suitable for drinking, the purity of which is unlikely to be suitable for use in the manufacture of pharmaceuticals.
Purified water	Vehicle and solvent for the manufacture of drug products and pharmaceutical preparations; not suitable for use in the manufacture of parenteral products.
Sterile water for inhalation	Diluent for inhalation therapy products.
Sterile water for injection	Diluent for injections.
Sterile water for irrigation	Diluent for internal irrigation therapy products.
Water for injections in bulk	Water for the bulk preparation of medicines for parenteral administration.

9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Boiling point: 100°C
Critical pressure: 22.1 MPa (218.3 atm)
Critical temperature: 374.2°C
Dielectric constant: $D^{25} = 78.54$
Dipole moment:
1.76 in benzene at 25°C;
1.86 in dioxane at 25°C.
Ionization constant: 1.008×10^{-14} at 25°C.
Latent heat of fusion: 6 kJ/mol (1.436 kcal/mol)
Latent heat of vaporization: 40.7 kJ/mol (9.717 kcal/mol)
Melting point: 0°C
Refractive index: $n_D^{20} = 1.3330$
Solubility: miscible with most polar solvents.
Specific gravity: 0.9971 at 25°C.
Specific heat (liquid): 4.184 J/g/°C (1.00 cal/g/°C) at 14°C.
Surface tension: 71.97 mN/m (71.97 dynes/cm) at 25°C.
Vapor pressure: 3.17 kPa (23.76 mmHg) at 25°C.
Viscosity (dynamic): 0.89 mPa s (0.89 cP) at 25°C.

11 Stability and Storage Conditions

Water is chemically stable in all physical states (ice, liquid, and vapor). Water for specific purposes should be stored in appropriate containers; *see* Table III.

Table II: Pharmacopeial specifications of water for different pharmaceutical applications.

Test	Water JP 2001	Purified water JP 2001	Purified water in bulk PhEur 2005	Purified water in containers PhEur 2005	Purified water USP 28	Water, highly purified PhEur 2005	Sterile water for injection USP 28	Bacteriostatic water for injection USP 28 Suppl. 1	Sterile water for inhalation USP 28 Suppl. 1	Sterile water for irrigation USP 28	Sterile purified water USP 28 Suppl. 1	Water for injection[a] JP 2001	Water for injection USP 28	Water for injection (in bulk) PhEur 2005	Sterile water for injection PhEur 2005	Sterile purified water JP 2001
Identification	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–
Production	–	–	+	–	–	+	–	–	–	–	–	–	–	+	–	–
Characters	+	+	+	+	–	+	–	–	–	–	–	–	–	+	–	+
Appearance of solution	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	+
Odor and taste	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	+
pH	5.8–8.6	–	–	–	–	–	5.0–7.0	4.5–7.0	4.5–7.5	5.0–7.0	5.0–7.0	–	5.0–7.0	–	–	–
Acid or alkali	–	+	–	+	–	–	–	–	–	–	–	+	–	–	+	+
Cadmium	⩽0.01 mg/L	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Chloride	⩽200 mg/L	+	–	+	–	–	+	–	+	+	+	+	+	–	+	+
Cyanide	⩽0.01 mg/L	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Copper	⩽1 mg/L	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Sulfate	–	+	–	+	–	–	+	+	+	+	+	+	+	–	+	+
Ammonium	⩽0.05 mg/L	⩽0.05 mg/L	–	⩽0.2 ppm	–	–	+	–	+	+	+	+	+	–	⩽0.2 ppm	⩽0.05 mg/L
Iron	⩽0.3 ppm	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Calcium	–	–	–	+	–	–	+	+	+	+	+	–	+	–	+	–
Lead	⩽0.1 mg/L	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Magnesium	–	–	–	+	–	–	–	–	–	–	–	–	–	–	+	–
Aluminum	–	–	⩽10 ppb	–	–	⩽10 ppb	–	–	–	–	–	–	–	⩽10 ppb	–	–
Nitrate	–	–	⩽0.2 ppm	–	–	⩽0.2 ppm	–	–	–	–	–	+	–	⩽0.2 ppm	⩽0.2 ppm	+
Nitrogen from nitrate	⩽10 mg/L	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Nitrogen from nitrite	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Carbon dioxide	–	–	–	–	–	–	+	+	+	+	+	–	+	–	–	–
Heavy metals	⩽1 mg/L	+	⩽0.1 ppm	+	–	⩽0.1 ppm	–	–	–	–	–	+	–	⩽0.1 ppm	+	+
Oxidizable substances	–	–	–	+	–	–	+	–	+	+	+	–	+	–	+	–
Potassium permanganate-reducing substances	⩽10 mg/L	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Residue on evaporation	⩽500 mg/L	⩽1.0 mg	–	⩽0.001%	–	–	–	–	–	–	–	+	–	–	+	⩽1.0 mg
Total organic carbon	–	–	–	–	+	⩽0.5 mg/L	–	–	–	–	–	+[b]	+	⩽0.5 mg/L	+	–
Total hardness	⩽300 mg/L	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Conductivity	–	–	+	–	+	+	–	–	–	–	–	–	+	+	⩽25 μS/cm for containers ⩽10 ml, ⩽5 μS/cm for containers ⩾10 ml	–
Anionic surfactants	⩽0.5 mg/L	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Antimicrobial agents	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–
Sterility	–	–	–	–	–	–	+	+	+	+	+	+	+	–	+	+
Particulate matter	–	–	–	–	–	–	+	+	–	–	–	–	–	–	+	–
Microbial contamination	+	–	–	⩽10^2/mL	–	–	–	–	–	–	–	–	–	–	–	–
Bacterial endotoxins	–	–	⩽0.25 IU/mL	⩽0.25 IU/mL	–	⩽0.25 IU/mL	⩽0.25 EU/mL	<0.5 EU/mL	<0.5 EU/mL	⩽0.25 EU/mL	–	⩽0.25 EU/mL	⩽0.25 EU/mL	⩽0.25 IU/mL	<0.25 IU/mL	–

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[a] For water for injection preserved in containers and sterilized, the JP 2001 provides separate tests for acid or alkali, chloride, ammonium, and residue on evaporation within the monograph.

[b] For water for injection prepared by reverse osmosis–ultrafiltration.

Table III: Storage requirements for different grades of water.

Type	Storage requirements[a]
Bacteriostatic water for injection	Preserve in single-dose and multiple-dose containers, preferably of Type I or Type II glass, not larger than 30 mL in size.
Potable water	Preserve in tightly sealed containers.
Purified water	Preserve in tightly sealed containers. If it is stored in bulk, the conditions of storage should be designed to limit the growth of microorganisms and avoid any other contamination.
Sterile water for inhalation	Preserve in single-dose containers, preferably of Type I or Type II glass.
Sterile water for injection	Preserve in single-dose containers, preferably of Type I or Type II glass, not more than 1000 mL in size.
Water for injection	Preserve in tightly sealed containers.
Water for injections in bulk	Collect and store in conditions designed to prevent growth of microorganisms and avoid any other contamination.

[a] To prevent evaporation and to maintain quality.

12 Incompatibilities

In pharmaceutical formulations, water can react with drugs and other excipients that are susceptible to hydrolysis (decomposition in the presence of water or moisture) at ambient and elevated temperatures.

Water can react violently with alkali metals and rapidly with alkaline metals and their oxides, such as calcium oxide and magnesium oxide. Water also reacts with anhydrous salts to form hydrates of various compositions, and with certain organic materials and calcium carbide.

13 Method of Manufacture

Unlike other excipients, water is not purchased from outside suppliers but is manufactured in-house by pharmaceutical companies. The selection of the most appropriate system and the overall design of the system are crucial factors to ensure that water of the correct quality is produced.(1,2)

To produce potable or drinking water, insoluble matter is first removed from a water supply by coagulation, settling, and filtering processes. Pathogenic microorganisms present are then destroyed by aeration, chlorination, or some other means. Water may also be rendered free of viable pathogenic microorganisms by active boiling for 15–20 minutes. Finally, the palatability of the water is improved by aeration and charcoal filtration.

The quality attributes of water for injection (WFI) are stricter than for purified water. Consequently, the preparation methods typically vary in the last stage to ensure good control of quality of WFI. Methods for the production of WFI are the subject of current debate. The PhEur 2005 indicates that only distillation would give assurance of consistent supply of the appropriate quality. However, the PhEur 2005 permits distillation, ion exchange, reverse osmosis, or any other suitable method that complies with regulations on water intended for human consumption laid down by the competent authority.

The USP 28 and the JP 2001 permit the use of reverse osmosis (RO) in addition to distillation and ultrafiltration. Purified water suitable for use in pharmaceutical formulations is usually prepared by purifying potable water by one of several processes, such as distillation; deionization; or reverse osmosis.(1,3–8)

Distillation A wide variety of stills are available to produce purified or distilled water. A typical design consists of an evaporator, vapor separator, and compressor. The distilland (raw feed water) is heated in the evaporator to boiling and the vapor produced is separated from entrained distilland in the separator. The vapor then enters a compressor where the temperature of the vapors is raised to 107°C. Superheated vapors are then condensed on the outer surface of the tubes of the evaporator containing cool distilland circulating within.

Vapor compression stills of various sizes are commercially available and can be used to produce water of high purity when properly constructed. A high-quality distillate, such as water for injection, can be obtained if the water is first deionized. The best stills are constructed of types 304 or 316 stainless steel and coated with pure tin, or are made from chemical-resistant glass.

De-ionization Cationic and anionic ion exchange resins are used to purify potable water by removing any dissolved ions. Dissolved gases are also removed, while chlorine, in the concentrations generally found in potable water, is destroyed by the resin itself. Some organics and colloidal particles are removed by adsorption and filtration. Resin beds may, however, foster microbial life and produce pyrogenic effluent unless adequate precautions are taken to prevent contamination. Mixed-bed units produce purer water (lower conductivity) than do stills. However, the organic matter content is usually higher. Ion exchange units are normally used today to treat raw feed water prior to distillation or reverse osmosis processing.

Reverse osmosis Water is forced through a semipermeable membrane in the opposite direction to normal osmotic diffusion. A very small proportion of inorganic salts passes through, but undissolved materials (bacteria and large molecules such as viruses, pyrogens, and high-molecular-weight organics) are removed.

Ultrafiltration A permeable membrane is used for mechanical separation. Impurities including endotoxins are removed by the membrane.

14 Safety

Water is the base for many biological life forms, and its safety in pharmaceutical formulations is unquestioned provided it meets standards of quality for potability(9) and microbial content; *see* Sections 9 and 18. Plain water is considered slightly more toxic upon injection into laboratory animals than physiological salt solutions such as normal saline or Ringer's solution.

Ingestion of excessive quantities of water can lead to water intoxication, with disturbances of the electrolyte balance.

Water for injection should be free from pyrogens.

LD_{50} (mouse, IP): 25 g/kg(10)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Included in nonparenteral and parenteral medicines licensed in the UK and USA.

17 Related Substances

Bacteriostatic water for injection; carbon dioxide-free water; de-aerated water; hard water; soft water; sterile water for inhalation; sterile water for injection; sterile water for irrigation; water for injection.

Bacteriostatic water for injection

Comments: the USP 28 (Suppl. 1.0) describes bacteriostatic water for injection as sterile water for injection that contains one or more suitable antimicrobial agents.

Carbon dioxide-free water

Comments: purified water that has been boiled vigorously for 5 minutes and allowed to cool while protecting it from absorption of atmospheric carbon dioxide.

De-aerated water

Comments: purified water that has been boiled vigorously for 5 minutes and cooled to reduce the air (oxygen) content.

Hard water

Comments: water containing the equivalent of not less than 120 mg/L and not more than 180 mg/L of calcium carbonate.

Soft water

Comments: water containing the equivalent of not more than 60 mg/L of calcium carbonate.

Sterile water for inhalation

Comments: the USP 28 (Suppl. 1.0) describes sterile water for inhalation as water purified by distillation or by reverse osmosis and rendered sterile. It contains no antimicrobial agents or other added substances, except where used in humidifiers or other similar devices, and where liable to contamination over a period of time.

Sterile water for injection

Comments: the USP 28 describes sterile water for injection as water for injection sterilized and suitably packaged. It contains no antimicrobial agents or other substances.

Sterile water for irrigation

Comments: the USP 28 describes sterile water for irrigation as water for injection sterilized and suitably packaged. It contains no antimicrobial agents or other substances.

Water for injection

Comments: the USP 28 describes water for injection as water purified by distillation or reverse osmosis. It contains no added substances. The PhEur 2005 title is 'water for injections' and comprises two parts: 'water for injections in bulk' and 'sterilized water for injection.' The PhEur 2005 states that water for injections is produced by distillation.

18 Comments

In most pharmacopeias, the term 'water' now refers to purified or distilled water.

Without further purification, 'water' may be unsuitable for certain pharmaceutical applications; for example, the presence of calcium in water affects the viscosity and gel strength of algins and pectin dispersions, while the use of potable water affects the clarity and quality of cough mixtures, and the stability of antibiotic liquid preparations.

Water commonly contains salts of aluminum, calcium, iron, magnesium, potassium, sodium, and zinc. Toxic substances such as arsenic, barium, cadmium, chromium, cyanide, lead, mercury, and selenium may constitute a danger to health if present in excessive amounts. Ingestion of water containing high amounts of calcium and nitrate is also contraindicated. National standards generally specify the maximum limits for these inorganic substances in potable water. Limits have also been placed on microorganisms, detergents, phenolics, chlorinated phenolics, and other organic substances. The WHO(11) and national bodies have issued guidelines for water quality, although many countries have their own standards for water quality embodied in specific legislation.(12) *See* Table IV.

Control of microbiological contamination is critical for waters used in preparation of pharmaceuticals as proliferation of microorganisms can potentially occur during all stages of manufacture, storage, or distribution. Suitable control is achieved by ensuring that the water system is well designed and well maintained. Purified water that is produced, stored, and circulated at ambient temperatures is susceptible to the establishment of biofilms; therefore, frequent monitoring, high usage, correct flow rate, and appropriate sanitization are all factors that require consideration to ensure that water is satisfactory.(13)

Table IV: Limits for inorganic substances in potable water (mg/L).

Contaminant	UK (mg/L)	WHO (mg/L)
Aluminum	0.2	0.2
Ammonium	0.5	—
Antimony	0.01	—
Arsenic	0.05	0.05
Barium	1.0	No limit
Beryllium	—	No limit
Boron	2.0	—
Cadmium	0.005	0.005
Calcium	250	—
Chloride	400	250
Chromium	0.05	0.05
Copper	3.0	1.0
Cyanide	0.05	0.1
Fluoride	1.5	1.5
Iron	0.2	0.3
Lead	0.05	0.05
Magnesium	50	—
Manganese	0.05	0.1
Mercury	0.001	0.001
Nickel	0.05	No limit
Nitrate (as N)	—	10
Nitrate (as NO_3)	50	—
Nitrite (as NO_2)	0.1	—
Phosphorus	2.2	—
Potassium	12	—
Selenium	0.01	0.01
Silver	0.01	No limit
Sodium	150	200
Sulfate	250	400
Zinc	5.0	5.0

Monitoring of the whole system is essential in order to demonstrate that correct microbiological quality is achieved. For WFI the recommended methodology is membrane filtration (0.45 μm) as a large sample size (100–300 mL) is required. For purified water, membrane filtration or plate count methods are typically used depending on the quality requirements of the system. It is important to set appropriate target, alert, and action limits to serve as an indication of action required to bring the quality of water back under control. It is recognized that limits are not intended as pass/fail criteria for water or product batches; however, an investigation regarding the implications should be conducted.(14)

Validation is conducted to provide a high level of assurance that the water production and distribution system will consistently produce water conforming to a defined quality specification. The validation process serves to qualify the design (DQ), installation (IQ), operation (OQ), and performance (PQ) of the system. The extent of monitoring data required should be defined, with consideration given to whether validation to FDA guidelines is required.(14) It is also important to have an ongoing control program with respect to maintenance and periodic reviews of the performance of the water system.

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21 Authors

LY Galichet.

22 Date of Revision

20 August 2005.

Wax, Anionic Emulsifying

1 Nonproprietary Names

BP: Emulsifying wax

2 Synonyms

Collone HV; *Crodex A*; *Cyclonette Wax*; *Lanette wax SX BP.*

3 Chemical Name and CAS Registry Number

Anionic emulsifying wax [8014-38-8]

4 Empirical Formula and Molecular Weight

The BP 2004 describes anionic emulsifying wax as containing cetostearyl alcohol, purified water, and either sodium lauryl sulfate or a sodium salt of a similar sulfated higher primary aliphatic alcohol. *See also* Sections 13 and 18.

5 Structural Formula

See Section 4.

6 Functional Categories

Emulsifying agent; stiffening agent.

7 Applications in Pharmaceutical Formulation or Technology

Anionic emulsifying wax is used in cosmetics and topical pharmaceutical formulations primarily as an emulsifying agent. The wax is added to fatty or paraffin bases to facilitate the production of oil-in-water emulsions that are nongreasy. In concentrations of about 2%, emulsions are pourable; stiffer emulsions, e.g., aqueous cream BP, may contain up to 10% of anionic emulsifying wax.

Creams should be adequately preserved and can usually be sterilized by autoclaving. A better-quality emulsion is produced by incorporating some alkali into the aqueous phase, although care should be taken not to use an excess.

Anionic emulsifying wax (3–30%) may also be mixed with soft and liquid paraffins to prepare anhydrous ointment bases such as emulsifying ointment BP. A preparation of 80% anionic emulsifying wax in white soft paraffin has been used as a soap substitute in the treatment of eczema.

In addition, anionic emulsifying wax (10%) has been added to theobroma oil to produce a suppository base with a melting point of 34°C.

8 Description

An almost white or pale yellow colored, waxy solid or flakes which when warmed become plastic before melting. Anionic emulsifying wax has a faint characteristic odor and a bland taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for anionic emulsifying wax.

Test	BP 2004
Identification	+
Characters	+
Acidity	+
Alkalinity	+
Alcohols	+
Iodine value	⩽3.0
Saponification value	⩽2.0
Sodium alkyl sulfates	⩾8.7%
Sulfated ash	2.5–4.0%
Unsaponifiable matter	⩾86.0%
Water	⩽4.0%

10 Typical Properties

Density: 0.97 g/cm^3

Flash point: >100°C

Melting point: 52°C

Solubility: soluble in chloroform, ethanol (95%), ether, and, on warming, in fixed oils and mineral oil; practically insoluble in water, forming an emulsion.

11 Stability and Storage Conditions

Solid anionic emulsifying wax is chemically stable and should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatibilities of anionic emulsifying wax are essentially those of sodium alkyl sulfates and include cationic compounds (quaternary ammonium compounds, acriflavine, ephedrine hydrochloride, antihistamines, and other nitrogenous compounds), salts of polyvalent metals (aluminum, zinc, tin, and lead), and thioglycollates. Anionic emulsifying wax is compatible with most acids above pH 2.5. It is also compatible with alkalis and hard water.

Iron vessels should not be used when heating anionic emulsifying wax; stainless steel containers are satisfactory.

13 Method of Manufacture

Anionic emulsifying wax is prepared by melting cetostearyl alcohol and heating to about 95°C. Sodium lauryl sulfate, or some other suitable anionic surfactant, and purified water are then added. The mixture is heated to 115°C and, while this temperature is maintained, the mixture is stirred vigorously until any frothing ceases. The wax is then rapidly cooled.

The BP 2004 specifies that the formula of anionic emulsifying wax is:

Cetostearyl alcohol	90 g
Sodium lauryl sulfate	10 g
Purified water	4 mL

14 Safety

Anionic emulsifying wax is used primarily in topical pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. However, sodium lauryl sulfate, a constituent of anionic emulsifying wax, is known to be irritant to the skin at high concentrations; sodium cetyl sulfate is claimed to be less irritating.

Emulsifying ointment BP, which contains anionic emulsifying wax, has been found to have major sunscreen activity in clinically normal skin and should therefore not be used before phototherapy procedures.(1)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended.

16 Regulatory Status

Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Cetostearyl alcohol; sodium lauryl sulfate; wax, nonionic emulsifying.

A number of emulsifying waxes are commercially available that contain different sodium alkyl sulfates and may not meet official compendial specifications. *See also* Section 18.

18 Comments

The nomenclature for emulsifying wax is confused since there are three groups of emulsifying waxes, with different titles in the UK and USA; *see* Table II.

Table II: Nomenclature for emulsifying wax.

	UK	USA
Nonionic	Cetomacrogol emulsifying wax	Emulsifying wax
Anionic	Emulsifying wax	—
Cationic	Cetrimide emulsifying wax	—

The waxes have similar physical properties but vary in the type of surfactant used, which, in turn, affects the range of compatibilities. Emulsifying wax BP and emulsifying wax USP contain anionic and nonionic surfactants, respectively, and are therefore not interchangeable in formulations.

19 Specific References

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20 General References

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21 Authors

AJ Winfield.

22 Date of Revision

15 August 2005.

Wax, Carnauba

1 Nonproprietary Names

BP: Carnauba wax
JP: Carnauba wax
PhEur: Cera carnauba
USPNF: Carnauba wax

2 Synonyms

Brazil wax; caranda wax; E903.

3 Chemical Name and CAS Registry Number

Carnauba wax [8015-86-9]

4 Empirical Formula and Molecular Weight

Carnauba wax consists primarily of a complex mixture of esters of acids and hydroxy acids, mainly aliphatic esters, ω-hydroxy esters, *p*-methoxycinnamic aliphatic esters, and *p*-hydroxycinnamic aliphatic diesters composed of several chain lengths, in which C_{26} and C_{32} alcohols are the most prevalent.(1)

Also present are acids, oxypolyhydric alcohols, hydrocarbons, resinous matter, and water.

5 Structural Formula

See Section 4.

6 Functional Category

Coating agent.

7 Applications in Pharmaceutical Formulation or Technology

Carnauba wax is widely used in cosmetics, certain foods, and pharmaceutical formulations. Cosmetically, carnauba wax is commonly used in lip balms.(2)

Carnauba wax is the hardest and highest-melting of the waxes commonly used in pharmaceutical formulations and is used primarily as a 10% w/v aqueous emulsion to polish sugar-coated tablets. Aqueous emulsions may be prepared by mixing carnauba wax with an ethanolamine compound and oleic acid. The carnauba wax coating produces tablets of good luster without rubbing. Carnauba wax may also be used in powder form to polish sugar-coated tablets.

Carnauba wax (10–50% w/w) is also used alone or with other excipients such as hypromellose, hydroxypropyl cellulose, alginate/pectin-gelatin, *Eudragit,* and stearyl alcohol to produce sustained-release solid-dosage formulations.(3–10)

Additionally, carnauba wax has been experimentally investigated for use in producing microparticles in a novel hot air coating (HAC) process developed as an alternative to conventional spray-congealing techniques.(11)

8 Description

Carnauba wax occurs as a light brown- to pale yellow-colored powder, flakes, or irregular lumps of a hard, brittle wax. It has a characteristic bland odor and practically no taste. It is free from rancidity. Various types and grades are available commercially.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for carnauba wax.

Test	JP 2001	PhEur 2005	USPNF 23
Characters	+	+	—
Identification	—	+	—
Appearance of solution	—	+	—
Melting range	80–86°C	80–88°C	80–86°C
Acid value	⩽10.0	2–7	2–7
Saponification value	78–95	78–95	78–95
Total ash	—	⩽0.25%	⩽0.25%
Heavy metals	—	—	⩽20 μg/g
Organic volatile impurities	—	—	+
Iodine value	5–14	—	—
Specific gravity	0.990–1.002	—	—

10 Typical Properties

Flash point: 270–330°C
Refractive index: $n_D^{90} = 1.450$
Solubility: soluble in warm chloroform and in warm toluene; slightly soluble in boiling ethanol (95%); practically insoluble in water.
Specific gravity: 0.990–0.999 at 25°C
Unsaponified matter: 50–55%

11 Stability and Storage Conditions

Carnauba wax is stable and should be stored in a well-closed container, in a cool, dry place.

12 Incompatibilities

—

13 Method of Manufacture

Carnauba wax is obtained from the leaf buds and leaves of the Brazilian carnauba palm, *Copernicia cerifera*. The leaves are dried and shredded and the wax is then removed by the addition of hot water.

14 Safety

Carnauba wax is widely used in oral pharmaceutical formulations, cosmetics, and certain food products. It is generally regarded as an essentially nontoxic and nonirritant material.(12–14)

There have been reports of allergic contact dermatitis from carnauba wax in mascara.(15)

The WHO has established an acceptable daily intake of up to 7 mg/kg body-weight for carnauba wax.(16)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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18 Comments

In cosmetics, carnauba wax is mainly used to increase the stiffness of formulations, e.g. lipsticks and mascaras.

The EINECS number for carnauba wax is 232-399-4.

19 Specific References

1 Emås M, Nyqvist H. Methods of studying aging and stabilization of spray-congealed solid dispersions with carnauba wax. 1: microcalorimetric investigation. *Int J Pharm* 2000; **197**: 117–127.

2 Marti-Mestres G, Nielland F, Rigal S, *et al.* Texture and sensory analysis in stick formulations. *STP Pharma Sci* 1999; **9**(4): 371–375.

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16 FAO/WHO. Evaluation of certain food additives and naturally occurring toxicants. Thirty-ninth report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1992; No. 828.

20 General References

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21 Authors

PJ Weller.

22 Date of Revision

5 April 2005.

Wax, Cetyl Esters

1 Nonproprietary Names

USPNF: Cetyl esters wax

2 Synonyms

Cera cetyla; *Crodamol SS*; *Cutina CP*; *Liponate SPS*; *Protachem MST*; *Ritaceti*; *Ritachol SS*; spermaceti wax replacement; *Starfol Wax CG*; *Synaceti 116*; synthetic spermaceti.

3 Chemical Name and CAS Registry Number

Cetyl esters wax [977067-67-6]

4 Empirical Formula and Molecular Weight

$C_nH_{2n}O_2$ where $n = 26–38. \approx 470–490$

The USPNF 23 describes cetyl esters wax as a mixture consisting primarily of esters of saturated fatty alcohols (C_{14}–C_{18}) and saturated fatty acids (C_{14}–C_{18}).

5 Structural Formula

See Section 4.

6 Functional Category

Emollient; stiffening agent.

7 Applications in Pharmaceutical Formulation or Technology

Cetyl esters wax is a stiffening agent and emollient used in creams and ointments as a replacement for naturally occurring spermaceti.

Cetyl esters wax is hydrophobic and has been proposed as a suitable component of an ophthalmic gelatin-based, controlled-release delivery matrix.(1)

The physical properties of cetyl esters wax vary greatly from manufacturer to manufacturer owing to differences between the mixtures of fatty acids and fatty alcohol esters that are used. Differences between products appear most obviously in the melting point, which can range from 43–47°C (USPNF 23 range) to 51–55°C, depending on the mixture. Materials with a high melting point tend to contain predominantly cetyl and stearyl palmitates. *See* Table I.

Table I: Uses of cetyl esters wax.

Use	Concentration (%)
Cold cream	12.5
Rose water ointment	12.5
Spermaceti ointment	20.0
Topical creams and ointments	1–15

8 Description

Cetyl esters wax occurs as white to off-white, somewhat translucent flakes (typically in the range of 5 μm to several millimeters in the largest dimension), having a crystalline structure and a pearly luster when caked. It has a faint, aromatic odor and a bland, mild taste.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for cetyl esters wax.

Test	USPNF 23
Melting range	43–47°C
Acid value	$\leqslant 5$
Iodine value	$\leqslant 1$
Saponification value	109–120
Paraffin and free acids	+

10 Typical Properties

Dielectric constant: 6–18
Flash point: >240°C
Peroxide value: $\leqslant 0.5$
Refractive index: $n_D^{60} = 1.440$
Solubility: high melting materials tend to be less soluble. *See* Table III.

Table III: Solubility of cetyl esters wax.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	1 in 500
Chloroform	1 in 2.5
Dichloromethane	1 in 3
Ethanol	1 in 170
Ethanol (95%)	Practically insoluble 1 in 2.5 at 78°C
Ether	Soluble
Ethyl acetate	1 in 80
Fixed and volatile oils	Soluble
Hexane	1 in 8
Mineral oil	1 in 70
Water	Practically insoluble

Specific gravity: 0.820–0.840 at 50°C
Viscosity (dynamic): 6.7–7.4 mPa s (6.7–7.4 cP) at 100°C

11 Stability and Storage Conditions

Store in a well-closed container in a cool, dry place. Avoid exposure to excessive heat (above 40°C).

12 Incompatibilities

Incompatible with strong acids or bases.

13 Method of Manufacture

Cetyl esters wax is prepared by the direct esterification of the appropriate mixtures of fatty alcohols and fatty acids.

14 Safety

Cetyl esters wax is an innocuous material generally regarded as essentially nontoxic and nonirritant.

LD_{50} (rat, oral): >16 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Spermaceti wax.

Spermaceti wax

CAS number: [8002-23-1]
Appearance: spermaceti is a waxy substance obtained from the head of the sperm whale. It consists of a mixture of the cetyl esters of fatty acids (C_{12}–C_{18}) with cetyl laurate, cetyl myristate, cetyl palmitate, and cetyl stearate comprising at least 85% of the total esters. It occurs as white, translucent, slightly unctuous masses with a faint odor and mild, bland taste.
Iodine value: 3.0–4.4
Melting point: 44–52°C
Refractive index: n_D^{80} = 1.4330
Saponification value: 120–136
Solubility: soluble in chloroform, boiling ethanol (95%), ether, and fixed or volatile oils; practically insoluble in ethanol (95%) and water.
Specific gravity: 0.938–0.944
Uses: spermaceti has been used in creams, ointments, and suppositories,⁽²⁾ although it has largely been superseded in pharmaceutical and cosmetics formulation by the synthetic material, cetyl esters wax.
Comments: the EINECS number for spermaceti wax is 232-302-5.

18 Comments

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19 Specific References

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2. Baichwal MR, Lohit TV. Medicament release from fatty suppository bases. *J Pharm Pharmacol* 1970; **22**: 427–432.

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21 Authors

PJ Weller.

22 Date of Revision

18 February 2005.

Wax, Microcrystalline

1 Nonproprietary Names

USPNF: Microcrystalline wax

2 Synonyms

Amorphous wax; E907; petroleum ceresin; petroleum wax (microcrystalline).

3 Chemical Name and CAS Registry Number

Microcrystalline wax [63231-60-7]

4 Empirical Formula and Molecular Weight

Microcrystalline wax is composed of a mixture of straight-chain and randomly branched saturated alkanes obtained from petroleum. The carbon chain lengths range from C_{41} to C_{57}; cyclic hydrocarbons are also present.

5 Structural Formula

See Section 4.

6 Functional Category

Coating agent; controlled-release vehicle; stiffening agent.

7 Applications in Pharmaceutical Formulation or Technology

Microcrystalline wax is used mainly as a stiffening agent in topical creams and ointments.

The wax is used to modify the crystal structure of other waxes (particularly paraffin wax) present in a mixture so that changes in crystal structure, usually exhibited over a period of time, do not occur. Microcrystalline wax also minimizes the sweating or bleeding of oils from blends of oils and waxes. Microcrystalline wax generally has a higher melting point than paraffin wax, and higher viscosity when molten, thereby increasing the consistency of creams and ointments when incorporated into such formulations.

Microcrystalline wax is also used in oral controlled-release matrix pellet formulations for various active compounds(1–3) and as a tablet- and capsule-coating agent. In controlled-release systems, microcrystalline wax coatings can also be used to affect the release of drug from ion-exchange resin beads.(4)

Microcrystalline wax is also used in confectionery, cosmetics, and food products.

8 Description

Microcrystalline wax occurs as odorless and tasteless waxy lumps or flakes containing small irregularly shaped crystals. It may vary in color from white to yellow, amber, brown, or black depending on the grade of material; pharmaceutical grades are usually white or yellow.

The USPNF 23 describes microcrystalline wax as a mixture of straight-chain, branched-chain, and cyclic hydrocarbons, obtained by solvent fractionation of the still-bottom fraction of petroleum by suitable means of dewaxing or de-oiling.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for microcrystalline wax.

Test	USPNF 23
Color	+
Melting range	54–102°C
Consistency	3–100
Acidity	+
Alkalinity	+
Residue on ignition	⩽0.1%
Organic acids	+
Fixed oils, fats, and rosin	+
Organic volatile impurities	+

10 Typical Properties

Acid value: 1.0
Density: 0.928–0.941 g/cm^3
Freezing point: 60.0–75.0°C
Refractive index: n_D^{100} = 1.435–1.445
Saponification value: 0.05–0.10
Solubility: soluble in benzene, chloroform, and ether; slightly soluble in ethanol; practically insoluble in water. When melted, microcrystalline wax is miscible with volatile oils and most warm fixed oils.
Viscosity (dynamic): 10.0–30.0 mPa s (10.0–30.0 cP) at 100°C.

11 Stability and Storage Conditions

Microcrystalline wax is stable in the presence of acids, alkalis, light, and air. The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

—

13 Method of Manufacture

Microcrystalline wax is obtained by solvent fractionation of the still-bottom fraction of petroleum by suitable dewaxing or de-oiling.

14 Safety

Microcrystalline wax is mainly used in topical pharmaceutical formulations but is also used in some oral products. It is generally regarded as a nontoxic and nonirritating material.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Paraffin.

18 Comments

Rheological studies of a model ointment containing microcrystalline wax, white petroleum, and mineral oil showed that while the latter two substances control the rheology of the ointment, microcrystalline wax incorporates itself into the existing white petroleum structure and builds up the structure of the ointment.(5)

19 Specific References

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20 General References

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21 Authors

AH Kibbe.

22 Date of Revision

5 April 2005.

Wax, Nonionic Emulsifying

1 Nonproprietary Names

BP: Cetomacrogol emulsifying wax
USPNF: Emulsifying wax

2 Synonyms

Collone NI; *Crodex N*; *Emulgade 1000NI*; *Permulgin D*; *Polawax*; *Ritachol 2000*; *T-Wax*.

3 Chemical Name and CAS Registry Number

Nonionic emulsifying wax [977069-99-0]

4 Empirical Formula and Molecular Weight

The USPNF 23 designates nonionic emulsifying wax as emulsifying wax that is prepared from cetostearyl alcohol and contains a polyoxyethylene derivative of a fatty acid ester of sorbitan. However, the BP 2004 describes nonionic emulsifying wax as cetomacrogol emulsifying wax prepared from cetostearyl alcohol and macrogol cetostearyl ether (22) (cetomacrogol 1000). The UK and US materials are therefore constitutionally different. *See also* Section 18.

5 Structural Formula

See Section 4.

6 Functional Category

Emulsifying agent; stiffening agent.

7 Applications in Pharmaceutical Formulation or Technology

Nonionic emulsifying wax is used as an emulsifying agent in the production of oil-in-water emulsions that are unaffected by moderate concentrations of electrolytes and are stable over a wide pH range. The concentration of wax used alters the consistency of a product owing to its 'self-bodying action'; at concentrations up to about 5% a product is pourable.

Concentrations of about 15% of nonionic emulsifying wax are commonly used in creams, but concentrations as high as 25% may be employed, e.g., in chlorhexidine cream BP. Nonionic emulsifying wax is particularly recommended for use with salts of polyvalent metals and medicaments based on nitrogenous compounds. Creams are susceptible to microbial spoilage and should be adequately preserved.

Nonionic emulsifying wax is also used in nonaqueous ointment bases, such as cetomacrogol emulsifying ointment BP, and in barrier creams.

8 Description

Nonionic emulsifying wax is a white or off-white waxy solid or flakes which melt when heated to give a clear, almost colorless liquid. Nonionic emulsifying wax has a faint odor characteristic of cetostearyl alcohol.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for nonionic emulsifying wax.

Test	BP 2004	USPNF 23
Identification	+	—
Characters	+	—
Melting range	—	50–54°C
Solidifying point	45–53°C	—
pH (3% dispersion)	—	5.5–7.0
Alkalinity	+	—
Acid value	⩽0.5	—
Hydroxyl value	175–192	178–192
Iodine value	—	⩽3.5
Refractive index (at 60°C)	1.435–1.439	—
Saponification value	⩽2.0	⩽14
Sulfated ash	⩽0.1%	—

10 Typical Properties

Density: 0.94 g/cm^3
Flash point: >55°C
Solubility: freely soluble in aerosol propellants, chloroform, and hydrocarbons; moderately soluble in ethanol (96%); partly soluble in ether and insoluble in water (forms emulsions).

11 Stability and Storage Conditions

Nonionic emulsifying wax is stable and should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Nonionic emulsifying wax is incompatible with tannin, phenol and phenolic materials, resorcinol, and benzocaine. It may reduce the antibacterial efficacy of quaternary ammonium compounds.

13 Method of Manufacture

The BP 2004 specifies that cetomacrogol emulsifying wax (nonionic emulsifying wax) may be prepared by melting and mixing together 800 g of cetostearyl alcohol and 200 g of macrogol cetostearyl ether (22) (cetomacrogol 1000). The mixture is then stirred until cold.

The USPNF 23 formula for nonionic emulsifying wax is a mixture of unstated proportions of cetostearyl alcohol and a polyoxyethylene derivative of a fatty acid ester of sorbitan.

14 Safety

Nonionic emulsifying wax is used in cosmetics and topical pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (topical aerosols, emulsions, lotions, and ointments). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Cationic emulsifying wax; cetostearyl alcohol; polyoxyethylene alkyl ethers; wax, anionic emulsifying.

It should be noted that there are many similar nonionic emulsifying waxes composed of different nonionic surfactants and fatty alcohols.

Cationic emulsifying wax

Synonyms: *cetrimide emulsifying wax*; *Crodex C.*

Method of manufacture: cetrimide emulsifying wax is prepared similarly to nonionic emulsifying wax and contains 90 g of cetostearyl alcohol and 10 g of cetrimide.

Comments: cationic emulsifying wax is claimed to be of particular value in cosmetic and pharmaceutical formulations when cationic characteristics are important. Thus it can be used in medicated creams, germicidal creams, ointments and lotions, hair conditioners, baby creams, and skin care products in which cationic compounds are included. Cationic emulsifying wax is compatible with cationic and nonionic materials, but is incompatible with anionic surfactants and drugs. Additional antimicrobial preservatives should be included in creams. Cetrimide may cause irritation to the eye; *see* Cetrimide.

18 Comments

The nomenclature for emulsifying wax is confused since there are three groups of emulsifying waxes with different titles in the UK and USA; *see* Table II.

Table II: Nomenclature for emulsifying wax.

	UK	USA
Nonionic	Cetomacrogol emulsifying wax	Emulsifying wax
Anionic	Emulsifying wax	—
Cationic	Cetrimide emulsifying wax	—

The waxes have similar physical properties but vary in the type of surfactant used, which, in turn, affects the range of compatibilities. Emulsifying wax BP and emulsifying wax USP contain anionic and nonionic surfactants, respectively, and are therefore not interchangeable in formulations.

19 Specific References

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20 General References

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21 Authors

AJ Winfield.

22 Date of Revision

15 August 2005.

Wax, White

1 Nonproprietary Names

BP: White beeswax
JP: White beeswax
PhEur: Cera alba
USPNF: White wax

2 Synonyms

Bleached wax; E901.

3 Chemical Name and CAS Registry Number

White beeswax [8012-89-3]

4 Empirical Formula and Molecular Weight

White wax is the chemically bleached form of natural beeswax; *see* Section 13.

Beeswax consists of 70–75% of a mixture of various esters of straight-chain monohydric alcohols with even-numbered carbon chains from C_{24} to C_{36} esterified with straight-chain acids. These straight-chain acids also have even numbers of carbon atoms up to C_{36} together with some C_{18} hydroxy acids. The chief ester is myricyl palmitate. Also present are free acids (about 14%) and carbohydrates (about 12%) as well as approximately 1% free wax alcohols and stearic esters of fatty acids.

5 Structural Formula

See Section 4.

6 Functional Category

Controlled-release vehicle; stabilizing agent; stiffening agent.

7 Applications in Pharmaceutical Formulation or Technology

White wax is a chemically bleached form of yellow wax and is used in similar applications: for example, to increase the consistency of creams and ointments, and to stabilize water-in-oil emulsions. White wax is used to polish sugar-coated tablets and to adjust the melting point of suppositories.

White wax is also used as a film coating in sustained-release tablets.(1)White beeswax microspheres may be used in oral dosage forms to retard the absorption of an active ingredient from the stomach, allowing the majority of absorption to occur in the intestinal tract. Wax coatings can also be used to affect the release of drug from ion-exchange resin beads.(2–4)

See also Yellow Wax.

8 Description

White wax consists of tasteless, white or slightly yellow-colored sheets or fine granules with some translucence. Its odor is similar to that of yellow wax but is less intense.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for white wax.

Test	JP 2001	PhEur 2005	USPNF 23
Characters	+	+	—
Drop point	60–67°C	61–66°C	62–65°C
Acid value	5–9 or 17–22	17–24	17–24
Ester value	—	70–80	72–79
Ester value : acid value ratio	—	3.3 : 4.3	—
Saponification value	80–100	87–104	+
Ceresin, paraffins, and certain other waxes	—	+	+
Glycerols and other polyols	—	+	+
Saponification cloud test	—	—	+
Purity	+	—	—
Relative density	—	≈0.960	—

10 Typical Properties

Arsenic: ⩽3 ppm
Density: 0.95–0.96 g/cm^3
Flash point: 245–258°C
Heavy metals: ⩽0.004%
Iodine number: 8–11
Lead: ⩽10 ppm
Melting point: 61–65°C
Peroxide value: ⩽8
Solubility: soluble in chloroform, ether, fixed oils, volatile oils, and warm carbon disulfide; sparingly soluble in ethanol (95%); practically insoluble in water.
Unsaponified matter: 52–55%

11 Stability and Storage Conditions

When the wax is heated above 150°C, esterification occurs with a consequent lowering of acid value and elevation of melting point. White wax is stable when stored in a well-closed container, protected from light.

12 Incompatibilities

Incompatible with oxidizing agents.

13 Method of Manufacture

Yellow wax (beeswax) is obtained from the honeycomb of the bee (*Apis mellifera* Linné (Fam. Apidae)); *see* Yellow Wax. Subsequent treatment with oxidizing agents bleaches the wax to yield white wax.

14 Safety

White wax is used in both topical and oral formulations, and is generally regarded as an essentially nontoxic and nonirritant material. However, although rare, hypersensitivity reactions to beeswax (attributed to contaminants in the wax) have been reported.(5,6)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets, rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Yellow wax.

18 Comments

—

19 Specific References

1 Nughroho AK, Fudholi A. Comparison of mefenamic acid dissolution in sustained release tablets using hydroxypropyl methylcellulose and cera alba as film coating. *Indonesian J Pharm* 1999; **10**(2): 78–84.

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3 Giannola LI, De Caro V, Rizzo MC. Preparation of white beeswax microspheres loaded with valproic acid and kinetic study of drug release. *Drug Dev Ind Pharm* 1995; **21**: 793–807.

4 Motycka S, Nairn J. Influence of wax coatings on release rate of anions from ion-exchange resin beads. *J Pharm Sci* 1978; **67**: 500–503.

5 Cronin E. Contact dermatitis from cosmetics. *J Soc Cosmet Chem* 1967; **18**: 681–691.

6 Rothenborg HW. Occupational dermatitis in beekeeper due to poplar resins in beeswax. *Arch Dermatol* 1967; **95**: 381–384.

20 General References

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21 Authors

AH Kibbe.

22 Date of Revision

5 April 2005.

Wax, Yellow

1 Nonproprietary Names

BP: Yellow beeswax
JP: Yellow beeswax
PhEur: Cera flava
USPNF: Yellow wax

2 Synonyms

Apifil; E901; refined wax.

3 Chemical Name and CAS Registry Number

Yellow beeswax [8012-89-3]

4 Empirical Formula and Molecular Weight

Yellow wax is naturally obtained beeswax; *see* Section 13.

Beeswax consists of 70–75% of a mixture of various esters of straight-chain monohydric alcohols with even-numbered carbon chains from C_{24} to C_{36} esterified with straight-chain acids. These straight-chain acids also have even numbers of carbon atoms up to C_{36} together with some C_{18} hydroxy acids. The chief ester is myricyl palmitate. Also present are free acids (about 14%) and carbohydrates (about 12%) as well as approximately 1% free wax alcohols and stearic esters of fatty acids.

5 Structural Formula

See Section 4.

6 Functional Category

Controlled-release vehicle; polishing agent; stabilizing agent; stiffening agent.

7 Applications in Pharmaceutical Formulation or Technology

Yellow wax is used in food, cosmetics, and confectionery products. Its main use is in topical pharmaceutical formulations, where it is used at a concentration of 5–20%, as a stiffening agent in ointments and creams. Yellow wax is also employed in emulsions because it enables water to be incorporated into water-in-oil emulsions.

In some oral formulations yellow wax is used as a polishing agent for sugar-coated tablets. It is also used in sustained-release formulations. Yellow wax coatings can be used to affect the release rate of drug from ion-exchange resin beads,(1) and has also been used in multiparticulate controlled-release dosage forms of chlorphenamine maleate.(2)

Yellow wax forms a soap with borax.

8 Description

Yellow or light brown pieces or plates with a fine-grained matt, noncrystalline fracture and a faint characteristic odor. The wax becomes soft and pliable when warmed.

The PhEur 2005 describes yellow wax as the wax obtained by melting the walls of the honeycomb made by the honeybee, *Apis mellifera*, with hot water and removing foreign matter.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for yellow wax.

Test	JP 2001	PhEur 2005	USPNF 23
Characters	+	+	—
Drop point	60–67°C	61–66°C	62–65°C
Relative density	—	≈0.960	—
Acid value	5–9 or 17–22	17–22	17–24
Ester value	—	70–80	72–79
Ester value : acid value ratio	—	3.3 : 4.3	—
Saponification value	80–100	87–102	—
Ceresin, paraffins, and certain other waxes	—	+	+
Purity	+	—	—
Glycerol and other polyols (as glycerol)	—	⩽0.5%	+
Saponification cloud test	—	—	+

10 Typical Properties

Acid value: 20
Arsenic: ⩽3 ppm
Density: 0.95–0.96 g/cm^3
Flash point: 245–258°C
Heavy metals: ⩽0.004%
Iodine number: 8–11
Lead: ⩽10 ppm
Melting point: 61–65°C
Peroxide value: ⩽8
Solubility: soluble in chloroform, ether, fixed oils, volatile oils, and warm carbon disulfide; sparingly soluble in ethanol (95%); practically insoluble in water.
Unsaponified matter: 52–55%
Viscosity (kinematic): 1470 mm^2/s (1470 cSt) at 99°C

11 Stability and Storage Conditions

When the wax is heated above 150°C esterification occurs with a consequent lowering of acid value and elevation of melting point. Yellow wax is stable when stored in a well-closed container, protected from light.

12 Incompatibilities

Incompatible with oxidizing agents.

13 Method of Manufacture

Yellow wax is a natural secretion of bees (*Apis mellifera* Linné (Fam. Apidae)) and is obtained commercially from honeycombs. Honey is abstracted from combs either by draining or centrifugation and water is added to the remaining wax to remove soluble impurities. Hot water is then added to form a floating melt, which is strained to remove foreign matter. The wax is then poured into flat dishes or molds to cool and harden.

14 Safety

Yellow wax is generally regarded as an essentially nontoxic and nonirritant material, and is used in both topical and oral formulations. However, hypersensitivity reactions attributed to contaminants in the wax, although rare, have been reported.(3,4)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets, and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

White wax.

18 Comments

Studies have shown that yellow wax, when added to suppository formulations, increased the melting point of the preparation significantly and decreased the rate of release of the active substance.(5)

19 Specific References

1 Motycka S, Nairn J. Influence of wax coatings on release rate of anions from ion-exchange resin beads. *J Pharm Sci* 1978; **67**: 500–503.
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4 Rothenborg HW. Occupational dermatitis in beekeeper due to poplar resins in beeswax. *Arch Dermatol* 1967; **95**: 381–384.
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20 General References

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21 Authors

AH Kibbe.

22 Date of Revision

5 April 2005.

Xanthan Gum

1 Nonproprietary Names

BP: Xanthan gum
PhEur: Xanthani gummi
USPNF: Xanthan gum

2 Synonyms

Corn sugar gum; E415; *Keltrol*; polysaccharide B-1459; *Rhodigel*; *Vanzan NF*; *Xantural*.

3 Chemical Name and CAS Registry Number

Xanthan gum [11138-66-2]

4 Empirical Formula and Molecular Weight

$(C_{35}H_{49}O_{29})_n$ Approximately 2×10^6

The USPNF 23 describes xanthan gum as a high molecular weight polysaccharide gum. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid, and is prepared as the sodium, potassium, or calcium salt.

5 Structural Formula

Each xanthan gum repeat unit contains five sugar residues: two glucose, two mannose, and one glucuronic acid. The polymer backbone consists of four β-D-glucose units linked at the 1 and 4 positions, and is therefore identical in structure to cellulose. Trisaccharide side chains on alternating anhydroglucose units distinguish xanthan from cellulose. Each side chain comprises a glucuronic acid residue between two mannose units. At most of the terminal mannose units is a pyruvate moiety; the mannose nearest the main chain carries a single group at C-6. The resulting stiff polymer chain may exist in solution as a single, double, or triple helix that interacts with other xanthan gum molecules to form complex, loosely bound networks.(1,2)

6 Functional Category

Stabilizing agent; suspending agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending and stabilizing agent.(3–5) It is also used as a thickening and emulsifying agent. It is nontoxic, compatible with most other pharmaceutical ingredients, and has good stability and viscosity properties over a wide pH and temperature range; *see* Section 11. Xanthan gum gels show pseudoplastic behavior, the shear thinning being directly proportional to the shear rate. The viscosity returns to normal immediately on release of shear stress.

When xanthan gum is mixed with certain inorganic suspending agents, such as magnesium aluminum silicate, or organic gums, synergistic rheological effects occur.(6) In general, mixtures of xanthan gum and magnesium aluminum silicate in ratios between 1 : 2 and 1 : 9 produce the optimum properties. Similarly, optimum synergistic effects are obtained with xanthan gum : guar gum ratios between 3 : 7 and 1 : 9.

Although primarily used as a suspending agent, xanthan gum has also been used to prepare sustained-release matrix tablets.(7–10) Controlled-release tablets of diltiazem hydrochloride prepared using xanthan gum have been reported to sustain the drug release in a predictable manner and the drug release profiles of these tablets were not affected by pH and agitation rate.(11)

Xanthan gum has been incorporated in an ophthalmic liquid dosage form, which interacts with mucin, thereby helping in the prolonged retention of the dosage form in the precorneal area.(12)

Recent studies have revealed that xanthan gum can also be used as an excipient for spray-drying and freeze-drying processes for better results.(13,14)

Xanthan gum can be used to increase the bioadhesive strength in vaginal formulations and as a binder in colon specific drug delivery systems.(15,16)

Xanthan gum is also used as a hydrocolloid in the food industry, and in cosmetics it has been used as a thickening agent in shampoo.(17)

8 Description

Xanthan gum occurs as a cream- or white-colored, odorless, free-flowing, fine powder.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for xanthan gum.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
pH	6.0–8.0	—
Viscosity	⩾600 mPas	⩾600 mPas
Propan-2-ol	⩽750 ppm	⩽0.075%
Other polysaccharides	+	—
Loss on drying	⩽15.0%	⩽15.0%
Total ash	6.5–16.0%	6.5–16.0%
Microbial contamination	+	+
Bacteria	⩽10^3/g	—
Fungi	⩽10^2/g	—
Pyruvic acid	—	⩽1.5%
Arsenic	—	⩽3 μg/g
Lead	—	⩽5 μg/g
Heavy metals	—	⩽0.003%
Organic volatile impurities	—	+
Assay	—	91.0–108.0%

10 Typical Properties

Acidity/alkalinity: pH = 6.0–8.0 for a 1% w/v aqueous solution.
Freezing point: 0°C for a 1% w/v aqueous solution.
Heat of combustion: 14.6 J/g (3.5 cal/g)
Melting point: chars at 270°C.
Particle size distribution: various grades with different particle sizes are available; for example, 100% less than 180 μm in size for *Keltrol CG*; 100% less than 75 μm in size for *Keltrol CGF*; 100% less than 250 μm, 95% less than 177 μm in size for *Rhodigel*; 100% less than 177 μm, 92% less than 74 μm in size for *Rhodigel 200*.
Refractive index: n_D^{20} = 1.333 for a 1% w/v aqueous solution.
Solubility: practically insoluble in ethanol and ether; soluble in cold or warm water.
Specific gravity: 1.600 at 25°C
Viscosity (dynamic): 1200–1600 mPa s (1200–1600 cP) for a 1% w/v aqueous solution at 25°C.

11 Stability and Storage Conditions

Xanthan gum is a stable material. Aqueous solutions are stable over a wide pH range (pH 3–12), although they demonstrate maximum stability at pH 4–10 and temperatures of 10–60°C. Xanthan gum solutions of less than 1% w/v concentration may be adversely affected by higher than ambient temperatures: for example, viscosity is reduced. Solutions are also stable in the presence of enzymes, salts, acids, and bases.

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Xanthan gum is an anionic material and is not usually compatible with cationic surfactants, polymers, or preservatives as precipitation occurs. Anionic and amphoteric surfactants at concentrations above 15% w/v cause precipitation of xanthan gum from a solution.

Under highly alkaline conditions, polyvalent metal ions such as calcium cause gelation or precipitation; this may be inhibited by the addition of a glucoheptonate sequestrant. The presence of low levels of borates (<300 ppm) can also cause gelation. This may be avoided by increasing the boron ion concentration or by lowering the pH of a formulation to less than pH 5. The addition of ethylene glycol, sorbitol, or mannitol may also prevent this gelation.

Xanthan gum is compatible with most synthetic and natural viscosity-increasing agents. If it is to be combined with cellulose derivatives, then xanthan gum free of cellulase should be used to prevent depolymerization of the cellulose derivative.

The viscosity of xanthan gum solutions is considerably increased, or gelation occurs, in the presence of some materials such as ceratonia, guar gum, and magnesium aluminum silicate.(6) This effect is most pronounced in deionized water and is reduced by the presence of salt. This interaction may be desirable in some instances and can be exploited to reduce the amount of xanthan gum used in a formulation; *see* Section 7.

Xanthan gum solutions are stable in the presence of up to 60% water-miscible organic solvents such as acetone, methanol, ethanol, or propan-2-ol. However, above this concentration precipitation or gelation occurs.

Xanthan gum is incompatible with oxidizing agents, some tablet film-coatings,(4) carboxymethylcellulose sodium,(18) dried aluminum hydroxide gel,(19) and some active ingredients such as amitriptyline, tamoxifen, and verapamil.(3)

13 Method of Manufacture

Xanthan gum is a polysaccharide produced by a pure-culture aerobic fermentation of a carbohydrate with *Xanthomonas campestris*. The polysaccharide is then purified by recovery with propan-2-ol, dried, and milled.(20,21)

14 Safety

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and food products and is generally regarded as nontoxic and nonirritant at the levels employed as a pharmaceutical excipient.

The estimated acceptable daily intake for xanthan gum has been set by the WHO at up to 10 mg/kg body-weight.(22)

LD_{50} (dog, oral): >20 g/kg(22)
LD_{50} (rat, oral): >45 g/kg
LD_{50} (mouse, oral): >1 g/kg(23)
LD_{50} (mouse, IP): >50 mg/kg(23)
LD_{50} (mouse, IV): 100–250 mg/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral solutions, suspensions, and tablets; rectal and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Ceratonia; guar gum.

18 Comments

Xanthan gum is available in several different grades that have varying particle sizes. Fine-mesh grades of xanthan gum are used in applications where high solubility is desirable since they dissolve rapidly in water. However, fine-mesh grades disperse more slowly than coarse grades and are best used dry blended with the other ingredients of a formulation. In general, it is preferable to dissolve xanthan gum in water first and then add the other ingredients of a formulation.

When added to liquid ophthalmics, xanthan gum delays the release of active substances, increasing the therapeutic activity of the pharmaceutical formulations.(24)

Xanthan gum has also been used to produce directly compressed matrices that display a high degree of swelling due to water uptake, and a small amount of erosion due to polymer relaxation.(25)

The USPNF 23 also includes a monograph for xanthan gum solution. A specification for xanthan gum is contained in the Food Chemicals Codex (FCC).

The EINECS number for xanthan gum is 234-394-2.

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KK Singh.

22 Date of Revision

7 August 2005.

Xylitol

1 Nonproprietary Names

BP: Xylitol
JP: Xylitol
PhEur: Xylitolum
USPNF: Xylitol

2 Synonyms

E967; *Klinit*; *meso*-xylitol; xilitol; *Xylifin*; *Xylisorb*; xylit; *Xylitab*; xylite; *Xylitolo*.

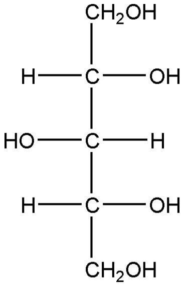
3 Chemical Name and CAS Registry Number

xylo-Pentane-1,2,3,4,5-pentol [87-99-0]

4 Empirical Formula and Molecular Weight

$C_5H_{12}O_5$ 152.15

5 Structural Formula



6 Functional Category

Antimicrobial preservative; base for medicated confectionery; coating agent; emollient; humectant; sweetening agent; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Xylitol is used as a noncariogenic sweetening agent in a variety of pharmaceutical dosage forms, including tablets, syrups, and coatings. It is also widely used as an alternative to sucrose in foods and confectionery. Xylitol is finding increasing application in chewing gum,(1,2) mouthrinses,(3) and toothpastes(4) as an agent that decreases dental plaque and tooth decay (dental caries). Unlike sucrose, xylitol is not fermented into cariogenic acid end products(5) and it has been shown to reduce dental caries by inhibiting the growth of cariogenic *Streptococcus mutans* bacteria.(6,7) As xylitol has an equal sweetness intensity to sucrose, combined with a distinct cooling effect upon dissolution of the crystal, it is highly effective in enhancing the flavor of tablets and syrups and masking the unpleasant or bitter flavors associated with some pharmaceutical actives and excipients.

In topical cosmetic and toiletry applications, xylitol is used primarily for its humectant and emollient properties, although it has also been reported to enhance product stability through a combination of potentiation of preservatives and its own bacteriostatic and bactericidal properties.

Granulates of xylitol are used as diluents in tablet formulations, where they can provide chewable tablets with a desirable sweet taste and cooling sensation, without the 'chalky' texture experienced with some other tablet diluents. Xylitol solutions are employed in tablet-coating applications at concentrations in excess of 65% w/w. Xylitol coatings are stable and provide a sweet-tasting and durable hard coating.

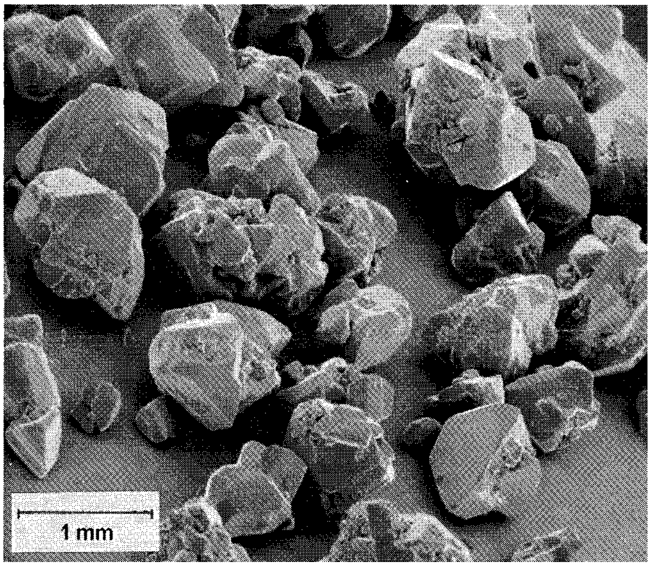
In liquid preparations, xylitol is used as a sweetening agent and vehicle for sugar-free formulations. In syrups, it has a reduced tendency to 'cap-lock' by effectively preventing crystallization around the closures of bottles. Xylitol also has a lower water activity and a higher osmotic pressure than sucrose, therefore enhancing product stability and freshness. In addition, xylitol has also been demonstrated to exert certain specific bacteriostatic and bactericidal effects, particularly against common spoilage organisms.(8,9)

Therapeutically, xylitol is additionally utilized as an energy source for intravenous infusion following trauma.(10)

8 Description

Xylitol occurs as a white, granular solid comprising crystalline, equidimensional particles having a mean diameter of about 0.4–0.6 mm. It is odorless, with a sweet taste that imparts a cooling sensation. Xylitol is also commercially available in powdered form and several granular, directly compressible forms.(11) *See also* Section 17.

SEM: 1
Excipient: Xylitol (unsieved)
Magnification: 60×



9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for xylitol.

Test	JP 2001	PhEur2005	USPNF 23
Identification	+	+	+
Characters	+	+	—
Clarity and color of solution	+	+	—
Water	⩽1.0%	⩽1.0%	⩽0.5%
pH (50% w/w solution)	5.0–7.0	—	—
Melting point	93.0–95.0°C	92–96°C	—
Residue on ignition	⩽0.1%	—	⩽0.5%
Chloride	⩽0.005%	—	—
Sulfate	⩽0.006%	—	—
Nickel	+	⩽1 ppm	—
Arsenic	⩽1.3 ppm	—	—
Heavy metals	⩽5 ppm	—	⩽0.001%
Reducing sugars (as dextrose)	+	⩽0.2%	⩽0.2%
Other polyols	—	—	⩽2.0%
Related substances	—	⩽2.0%	—
Lead	—	⩽0.5 ppm	—
Bacterial endotoxins[a]	—	⩽2.5 IU/g	—
Conductivity	—	⩽20 μS cm^{-1}	—
Organic volatile impurities	—	—	+
Assay (anhydrous basis)	⩾98.0%	98.0–102.0%	98.5–101.0%

[a] If intended for use in parenteral products.

10 Typical Properties

Acidity/alkalinity: pH = 5.0–7.0 (10% w/v aqueous solution).

Boiling point: 215–217°C

Compressibility: *see* Figure 1. Crystalline xylitol, under the same test conditions as illustrated in Figure 1, produces 12.5 mm tablets of 40 N hardness at 20 kN compression force.

Density (true): 1.52 g/cm^3

Density (bulk):

0.8–0.85 g/cm^3 for crystalline xylitol;

0.5–0.7 g/cm^3 for directly compressible granulated grades.

Flowability: flow characteristics vary depending upon the particle size of xylitol used. Fine-milled grades tend to be relatively poorly flowing, while granulated grades have good flow properties.

Heat of solution: −157.1 kJ/kg (–36.7 cal/g)

Melting point: 92.0–96.0°C

Moisture content: xylitol is a moderately hygroscopic powder under normal conditions; *see also* Figure 2. At 20°C and 52% relative humidity, the equilibrium moisture content of xylitol is 0.1% w/w. After drying in a vacuum, over P_2O_5 at 80°C for 4 hours, xylitol loses less than 0.5% w/w water.

Osmolarity: a 4.56% w/v aqueous solution is iso-osmotic with serum.

Particle size distribution: the particle size distribution of xylitol depends upon the grade selected. Normal crystalline material typically has a mean particle size of 0.4–0.6 mm. Milled grades are commercially available that offer mean particle sizes as low as 50 μm. Individual suppliers' literature should be consulted for further information. For particle size distributions of granulated xylitol, *see* Figure 3.

Solubility: *see* Table II.

Table II: Solubility of xylitol.

Solvent	Solubility at 20°C
Ethanol	1 in 80
Glycerin	Very slightly soluble
Methanol	1 in 16.7
Peanut oil	Very slightly soluble
Propan-2-ol	1 in 500
Propylene glycol	1 in 15
Pyridine	Soluble
Water	1 in 1.6

Specific rotation: not optically active.

Viscosity (dynamic): *see* Figure 4.

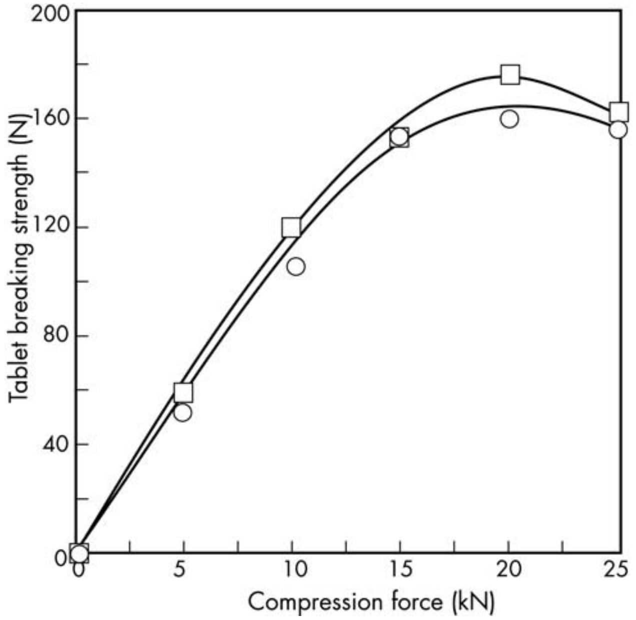


Figure 1: Compression characteristics of *Xylitab 100* and *Xylitab 200* (Danisco Sweeteners Ltd.).
○: Xylitol with 3.5% polydextrose (*Xylitab 100*)
□: Xylitol with 2.0% carboxymethylcellulose (*Xylitab 200*)

11 Stability and Storage Conditions

Xylitol is stable to heat but is marginally hygroscopic. Caramelization can occur only if it is heated for several minutes near its boiling point. Crystalline material is stable for at least 3 years if stored at less than 65% relative humidity and 25°C. Milled and specialized granulated grades of xylitol have a tendency to cake and should therefore be used within 6 months. Aqueous xylitol solutions have been reported to be stable, even on prolonged heating and storage. Since xylitol is not utilized by most microorganisms, products made with xylitol are usually safe from fermentation and microbial spoilage.(8,9)

Xylitol should be stored in a well-closed container in a cool, dry place.

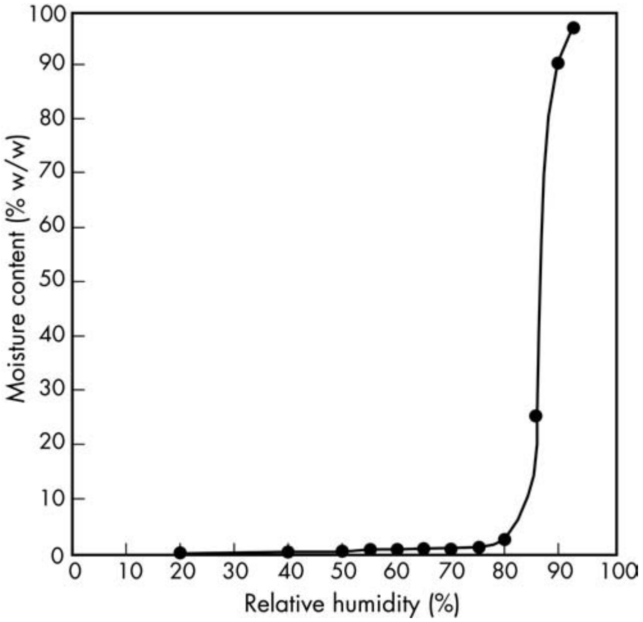


Figure 2: Moisture sorption isotherm of xylitol at 20°C.

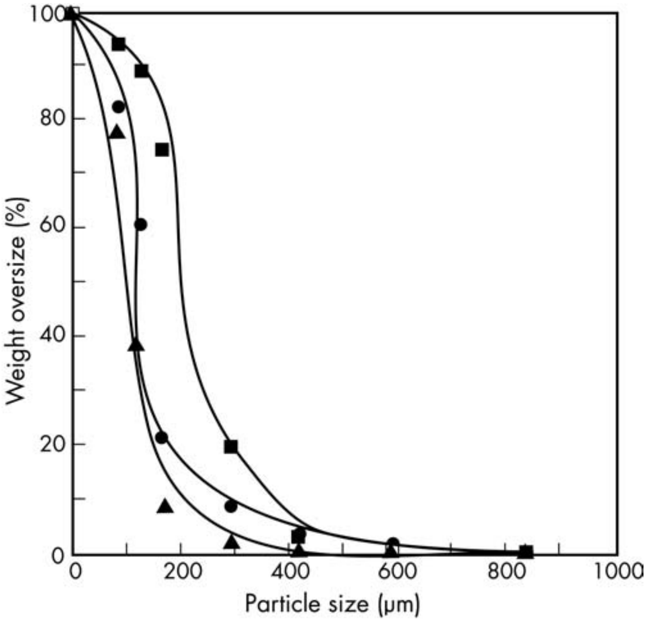


Figure 3: Particle size distribution of granulated xylitol (*Xylitab*, Danisco Sweeteners Ltd.).

●: *Xylitab 100* granulated with 3.5% polydextrose

■: *Xylitab 200* granulated with 2.0% carboxymethylcellulose

▲: *Xylitab* 300 wet granulated.

12 Incompatibilities

Xylitol is incompatible with oxidizing agents.

13 Method of Manufacture

Xylitol occurs naturally in many fruits and berries, although extraction from such sources is not considered to be commercially viable. Industrially, xylitol is most commonly derived from various types of hemicellulose obtained from such sources as wood, cane pulp, seed hulls, and shells. These materials usually contain 20–35% xylan, which is readily converted to xylose (wood sugar) by hydrolysis. This xylose is subsequently converted to xylitol via hydrogenation (reduction). Following the hydrogenation step, there are a number of separation and purification steps that ultimately yield high-purity xylitol crystals. The nature of this process, and the stringent purification procedures employed, result in a finished product with a very low impurity content. Potential impurities that may appear in small quantities are mannitol, sorbitol, galactitol, or arabitol.

Less commonly employed methods of xylitol manufacture include the conversion of glucose (dextrose) to xylose followed by hydrogenation to xylitol, and the microbiological conversion of xylose to xylitol.

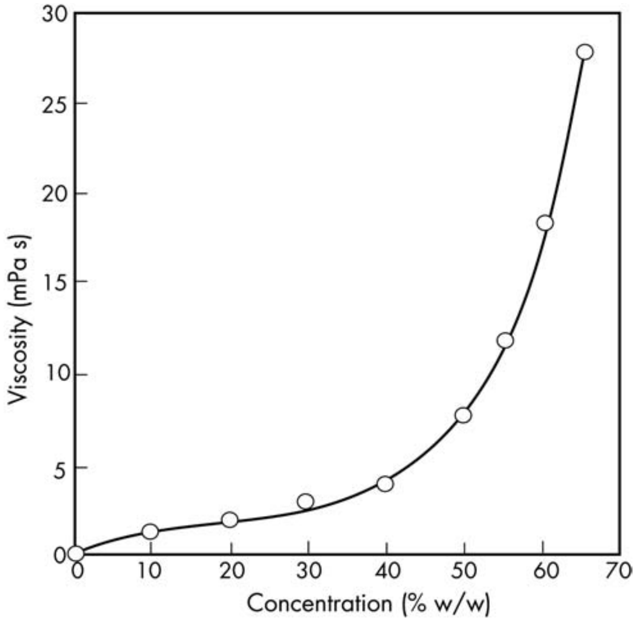


Figure 4: Viscosity of aqueous xylitol solutions at 20°C.

14 Safety

Xylitol is used in oral pharmaceutical formulations, confectionery, and food products and is generally regarded as an essentially nontoxic, nonallergenic, and nonirritant material.

Xylitol has an extremely low glycemic index and is metabolized independently of insulin. Following ingestion of xylitol, the blood glucose and serum insulin responses are significantly lower than following ingestion of glucose or sucrose. These factors make xylitol a suitable sweetener for use in diabetic or carbohydrate-controlled diets.(12)

Up to 100 g of xylitol in divided oral doses may be tolerated daily, although, as with other polyols, large doses may have a laxative effect. The laxative threshold depends on a number of factors, including individual sensitivity, mode of ingestion, daily diet, and previous adaptation to xylitol. Single doses of 20–30 g and daily doses of 0.5–1.0 g/kg bodyweight are usually well tolerated by most individuals. Approximately 25–50% of the ingested xylitol is absorbed, with the remaining 50–75% passing to the lower gut, where it undergoes indirect metabolism via fermentative degradation by the intestinal flora.

An acceptable daily intake for xylitol of 'not specified' has been set by the WHO since the levels used in foods do not represent a hazard to health.(13)

LD$_{50}$ (mouse, IP): 22.1 g/kg(14,15)
LD$_{50}$ (mouse, IV): 12 g/kg
LD$_{50}$ (mouse, oral): 12.5 g/kg
LD$_{50}$ (rat, oral): 17.3 g/kg
LD$_{50}$ (rat, IV): 10.8 g/kg
LD$_{50}$ (rabbit, oral): 16.5 g/kg
LD$_{50}$ (rabbit, IV): 4 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Xylitol may be harmful if ingested in large quantities; and may also be irritant to the eyes. Eye protection and gloves are recommended. Xylitol is flammable, but does not ignite readily.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral solution, chewing gum). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Various directly compressible forms of xylitol that contain other excipients are commercially available, e.g., *Xylitab 100*, which contains 3.5% polydextrose, and *Xylitab 200*, which contains 2.0% carboxymethylcellulose (both Danisco Sweeteners Ltd.). A directly compressible form of pure xylitol is also available, *Xylitab 300* (Danisco Sweeteners Ltd.), which is produced via wet granulation.

Pyrogen-free grades of xylitol suitable for parenteral use are also commercially available.

18 Comments

The sweetening power of xylitol is approximately equal to that of sucrose, although it has been shown to be pH-, concentration-, and temperature-dependent; xylitol is approximately 2.5 times as sweet as mannitol.

Xylitol is highly chemically stable, meaning that it will not interact with pharmaceutical actives or excipients, and can be utilized over a wide pH range (pH 1–11).

The EINECS number for xylitol is 201-788-0.

Xylitol has a negative heat of solution that is far larger than that of other alternative sweetening agents; *see* Table III. Because of this, xylitol produces an intense cooling effect as the crystalline material dissolves. Xylitol's combination of sweetness and cooling can create product appeal while helping to mask the undesirable taste of many pharmaceutical actives or excipients.

A specification for xylitol is contained in the Food Chemicals Codex (FCC).

19 Specific References

1 Tanzer JM. Xylitol chewing gum and dental caries. *Int Dent J* 1995; **45**(1): 65–76.
2 Soderling E, Trahan L, Tammiala T, Hakkinen L. Effects of xylitol, xylitol-sorbitol, and placebo chewing gums on the plaque of habitual xylitol consumers. *Eur J Oral Sci* 1997; **105**(2): 170–177.

Table III: Comparison of the heat of solution of selected sweetening agents.

Sweetening agent	Heat of solution (kJ/kg)
Lactitol (anhydrous)	−35.0
Maltitol	−69.2
Mannitol	−120.9
Sorbitol	−106.3
Sucrose	−23.0
Xylitol	−157.1

3 Cobanera A, Morasso A, White E, *et al.* Xylitol-sodium fluoride: effect on plaque. *J Dent Res* 1987; **66**: 814.
4 Sintes JL, Escalante C, Stewart B, *et al.* Enhanced anticaries efficacy of a 0.243% sodium fluoride/10% xylitol/silica dentifrice: 3-year clinical results. *Am J Dent* 1995; **8**(5): 231–235.
5 Trahan L. Xylitol: a review of its action on mutans streptococci and dental plaque – its clinical significance. *Int Dent J* 1995; **45**(1): 77–92.
6 Hayes C. The effect of non-cariogenic sweeteners on the prevention of dental caries: a review of the evidence. *J Dent Educ* 2001; **65**(10): 1106–1109.
7 Makinen KK, Chen CCY, Makinen PL, *et al.* Properties of whole saliva and dental plaque in relation to 40-month consumption of chewing gums containing xylitol, sorbitol and sucrose. *Caries Res* 1996; **30**(3): 180–188.
8 Emodi A. Xylitol: its properties and food applications. *Food Technol* 1978; **Jan**: 28–32.
9 Makinen KK, Soderling E. Effect of xylitol on some food spoilage microorganisms. *J Food Sci* 1981; **46**(3): 950–951.
10 Georgieff M, Moldawer LL, Bistrian BR, Blackburn GL. Xylitol, an energy source for intravenous nutrition after trauma. *J Parenter Enteral Nutr* 1985; **9**: 199–209.
11 Garr JSM, Rubinstein MH. Direct compression characteristics of xylitol. *Int J Pharm* 1990; **64**: 223–226.
12 Natah SS, Hussien KR, Touminen JA, Koivisto VA. Metabolic response to lactitol and xylitol in healthy men. *Am J Clin Nutr* 1997; **65**(4): 947–950.
13 FAO/WHO. Evaluation of certain food additives and contaminants. Twenty-seventh report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1983; No. 696.
14 Sweet DV, ed. *Registry of Toxic Effects of Chemical Substances.* Cincinnati: US Department of Health, 1987: 5127–5128.
15 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials,* 11th edn. New York: Wiley, 2004: 3707.

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Counsell JN. *Xylitol.* London: Applied Science Publishers, 1978.
O'Brien Nabors L, Gelardi RC, eds. *Alternative Sweeteners*, 2nd edn. New York: Marcel Dekker, 1991.
Thomas SE, Ali MA, Craig DQM, *et al.* The use of xylitol as a carrier for liquid-filled hard-gelatin capsules. *Pharm Technol Int* 1991; 3(9): 36–40.
Ylikahri R. Metabolic and nutritional aspects of xylitol. *Adv Food Res* 1979; **25**: 159–180.

21 Authors

M Bond.

22 Date of Revision

23 August 2005.

Zein

1 Nonproprietary Names

USPNF: Zein

2 Synonyms

—

3 Chemical Name and CAS Registry Number

Zein [9010-66-6]

4 Empirical Formula and Molecular Weight

Zein is a prolamin with a molecular weight of approximately 38 000.

5 Structural Formula

See Section 8.

6 Functional Category

Coating agent; extended-release agent; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Zein is used as a tablet binder in wet-granulation processes or as a tablet-coating agent mainly as a replacement for shellac. It is used primarily as an enteric-coating agent or in extended-release oral tablet formulations.(1) Zein is also used in food applications as a coating agent. *See* Table I.

Table I: Uses of zein.

Use	Concentration (%)
Tablet coating agent	15
Tablet sealer	20
Wet granulation binder	30

8 Description

Zein is a prolamin obtained from corn (*Zea mays* Linné (Fam. Gramineae)). It occurs as a granular, straw- to pale yellow-colored amorphous powder or fine flakes and has a characteristic odor and bland taste.

For amino acid composition, *see* Section 18.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for zein.

Test	USPNF 23
Identification	+
Microbial limits	$\leqslant$1000/g
Loss on drying	$\leqslant$8.0%
Residue on ignition	$\leqslant$2.0%
Heavy metals	$\leqslant$0.002%
Organic volatile impurities	+
Nitrogen content (dried basis)	13.1–17.0%

10 Typical Properties

Density: 1.23 g/cm^3

Melting point: when completely dry, zein may be heated to 200°C without visible signs of decomposition.

Particle size distribution: 100% less than 840 μm in size.

Solubility: practically insoluble in acetone, ethanol, and water; soluble in aqueous alcohol solutions, aqueous acetone solutions (60–80% v/v), and glycols. Also soluble in aqueous alkaline solutions of pH 11.5 and above.

11 Stability and Storage Conditions

Zein should be stored in an airtight container, in a cool, dry place. It has not been reported to polymerize.(2,3)

12 Incompatibilities

Incompatible with oxidizing agents.

13 Method of Manufacture

Zein is extracted from corn gluten meal with dilute propan-2-ol.

14 Safety

Zein is used in oral pharmaceutical formulations and food products and is generally regarded as an essentially nontoxic and nonirritant material at the levels employed as an excipient. However, it may be harmful if ingested in large quantities. *See also* Section 18.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Zein may be irritant to the eyes and may evolve toxic fumes on combustion. Eye-protection and gloves are recommended.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

—

18 Comments

The EINECS number for zein is 232-722-9.

Zein is a protein derivative that does not contain lysine or tryptophan. For the approximate amino acid content of zein, *see* Table III.

Zein may be safely consumed by persons sensitive to gluten.

A specification for zein is contained in the Food Chemicals Codex (FCC).

Table III: Approximate amino acid content of zein.

Alanine	8.3%	/Leucine	19.3%
Arginine	1.8%	Methionine	2.0%
Asparagine	4.5%	Phenylalanine	6.8%
Cystine	0.8%	Proline	9.0%
Glutamic acid	1.5%	Serine	5.7%
Glutamine	21.4%	Threonine	2.7%
Glycine	0.7%	Tyrosine	5.1%
Histidine	1.1%	Valine	3.1%
Isoleucine	6.2%		

19 Specific References

1 Katayama H, Kanke M. Drug release from directly compressed tablets containing zein. *Drug Dev Ind Pharm* 1992; **18**: 2173–2184.

2 Porter SC. Tablet coating. *Drug Cosmet Ind* 1996; **May**: 46–93.

3 Seitz JA, Mehta SP, Yeager JL. Tablet coating. In: Lachman L, Liebermann HA, Kanig JL, eds. *The Theory and Practice of Industrial Pharmacy*. Philadelphia: Lea and Febiger, 1986: 346–373.

20 General References

Beck MI, Tomka I, Waysek E. Physico-chemical characterization of zein as a film coating polymer: a direct comparison with ethyl cellulose. *Int J Pharm* 1996; **141**: 137–150.

21 Authors

O AbuBaker.

22 Date of Revision

5 August 2005.

Zinc Acetate

1 Nonproprietary Names

PhEur: Zinc acetas dihydricus
USP: Zinc acetate

2 Synonyms

Acetic acid, zinc salt; dicarbomethoxy zinc; zinc (II) acetate; zinc diacetate; zinc ethanoate.

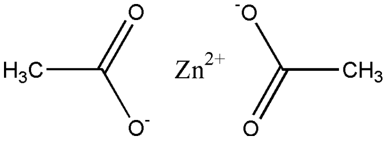
3 Chemical Name and CAS Registry Number

Zinc acetate dihydrate [5970-45-6]
Zinc acetate anhydrous [557-34-6]

4 Empirical Formula and Molecular Weight

$C_4H_6O_4Zn{\cdot}2H_2O$	219.50 (for dihydrate)
$C_4H_6O_4Zn$	183.47 (for anhydrous)

5 Structural Formula



6 Functional Category

Emollient; emulsion stabilizer; gelling agent; opacifier; stabilizing agent.

7 Applications in Pharmaceutical Formulation or Technology

Zinc acetate has been used as an excipient in a variety of pharmaceutical formulations including topical gels, lotions, and solutions, and subcutaneous injections. It has also been investigated for use in an oral controlled-release formulation for water-soluble drugs in combination with sodium alginate and xanthan gum.(1)

Therapeutically, zinc acetate has been used in oral capsules for the treatment of Wilson's disease.(2,3) Zinc acetate has also been demonstrated to be effective as a spermicide in vaginal contraceptives.(4)

8 Description

Zinc acetate occurs as white crystalline, lustrous plates with a faint acetic odor and an astringent taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for zinc acetate.

Test	PhEur 2005	USP 28
Identification	+	+
Appearance of solution	+	—
pH (5% w/v)	5.8–7.0	6.0–8.0
Reducing substances	+	—
Insoluble matter	—	+
Arsenic	⩽2 ppm	⩽3 ppm
Lead	⩽10 ppm	⩽0.002%
Chlorides	⩽50 ppm	⩽0.005%
Sulfates	⩽100 ppm	⩽0.010%
Aluminum	⩽5 ppm	—
Cadmium	⩽2 ppm	—
Copper	⩽50 ppm	—
Iron	⩽50 ppm	—
Alkalis and alkaline earths	—	⩽0.2%
Organic volatile impurities	—	+
Assay	99.0–101.0%	98.0–102.0%

10 Typical Properties

Acidity/alkalinity: pH = 6.0–8.0 (5% w/v aqueous solution of the dihydrate)
Boiling point: decomposes.
Melting point: 237°C
Solubility: for the dihydrate, *see* Table II.
Specific gravity: 1.735

Table II: Solubility of zinc acetate dihydrate.

Solvent	Solubility at 20°C unless otherwise stated
Ethanol (95%)	1 in 30 1 in 1 of boiling ethanol (95%)
Water	1 in 2.3 1 in 1.6 at 100°C

11 Stability and Storage Conditions

Zinc acetate loses water of hydration above 100°C. Zinc acetate should be stored in a well-closed container in a cool, dry, place.

12 Incompatibilities

Zinc acetate is incompatible with oxidizing agents, zinc salts, alkalis and their carbonates, oxalates, phosphates, and sulfides.(5)

13 Method of Manufacture

Zinc acetate is synthesized by reacting zinc oxide with glacial acetic acid, with subsequent crystallization, separation by centrifugation, and drying and milling of the crystals. No organic solvents are used during the synthesis.

14 Safety

Zinc acetate is used in topical pharmaceutical formulations and subcutaneous injections, where it is generally regarded as relatively nontoxic and nonirritant when used as an excipient. However, zinc acetate is poisonous by intravenous and intraperitoneal routes; it is also moderately toxic following oral consumption.(5)

Zinc acetate:
  LD_{50} (rat, oral): 2.510 g/kg(5)
  LD_{50} (IP, mouse): 0.057 g/kg
Zinc acetate dihydrate:
  LD_{50} (mouse, IP): 0.108 g/kg
  LD_{50} (mouse, oral): 0.287 g/kg
  LD_{50} (rat, IP): 0.162 g/kg
  LD_{50} (rat, oral): 0.794 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. When heated to decomposition, zinc acetate emits toxic fumes of zinc oxide.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (SC injections; topical lotions and solutions). Included in medicines licensed in the UK.

17 Related Substances

—

18 Comments

A specification for zinc acetate is included in the Japanese Pharmaceutical Excipients (JPE) 2004.(6) The EINECS number for zinc acetate is 209-170-2.

19 Specific References

1 Zeng WM. Oral controlled-release formulation for highly water-soluble drugs: drug–sodium alginate–xanthan gum–zinc acetate matrix. *Drug Dev Ind Pharm* 2004; **30**: 491–495.
2 Brewer GJ. Zinc acetate for the treatment of Wilson's disease. *Expert Opin Pharmacother* 2001; **2**: 1473–1477.
3 Fahim MS, Wang M. Zinc acetate and lyophilized *Aloe barbadensis* as vaginal contraceptive. *Contraception* 1996; **53**: 231–236.
4 European Medicines Evaluation Agency. Summary scientific opinion for the approval of Wilzin (zinc acetate dehydrate). http://www.emea.eu.int/humandocs/PDFs/EPAR/Wilzin/099104en6.pdf (accessed 12 April 2005).
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6 Japan Pharmaceutical Excipients Council. *Japanese Pharmaceutical Excipients 2004*. Tokyo: Yakuji Nippo, 2004: 945–946.

20 General References

—

21 Authors

LY Galichet

22 Date of Revision

24 August 2005

Zinc Stearate

1 Nonproprietary Names

BP: Zinc stearate
PhEur: Zinci stearas
USP: Zinc stearate

2 Synonyms

Cecavon; dibasic zinc stearate; *HyQual*; stearic acid zinc salt; zinc distearate; zinc soap.

3 Chemical Name and CAS Registry Number

Octadecanoic acid zinc salt [557-05-1]

4 Empirical Formula and Molecular Weight

$C_{36}H_{70}O_4Zn$ 632.33 (for pure material)

The USP 28 describes zinc stearate as a compound of zinc with a mixture of solid organic acids obtained from fats, and consists chiefly of variable proportions of zinc stearate and zinc palmitate. It contains the equivalent of 12.5–14.0% of zinc oxide (ZnO).

The PhEur 2005 states that zinc stearate $[(C_{17}H_{35}COO)_2Zn]$ may contain varying proportions of zinc palmitate $[(C_{15}H_{31}COO)_2Zn]$ and zinc oleate $[(C_{17}H_{33}COO)_2Zn]$. It contains not less than 10.0% and not more than 12.0% of zinc.

5 Structural Formula

See Section 4.

6 Functional Category

Tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Zinc stearate is primarily used in pharmaceutical formulations as a lubricant in tablet and capsule manufacture at concentrations up to 1.5% w/w. It has also been used as a thickening and opacifying agent in cosmetic and pharmaceutical creams and as a dusting powder. *See* Table I.

Table I: Uses of zinc stearate.

Use	Concentration (%)
Tablet lubricant	0.5–1.5
Water-repellent ointments	2.5

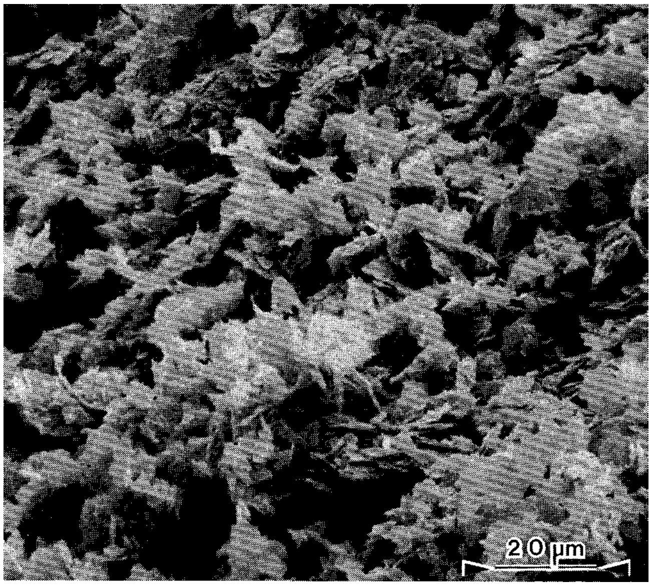
8 Description

Zinc stearate occurs as a fine, white, bulky, hydrophobic powder, free from grittiness and with a faint characteristic odor.

9 Pharmacopeial Specifications

See Table II.

SEM: 1
Excipient: Zinc stearate
Magnification: 600×



SEM: 2
Excipient: Zinc stearate
Magnification: 2400×

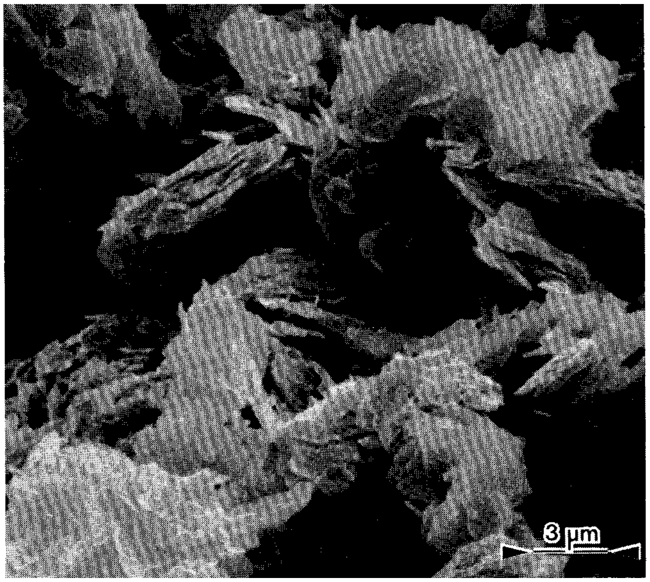


Table II: Pharmacopeial specifications for zinc stearate.

Test	PhEur 2005	USP 28
Identification	+	+
Characters	+	—
Acidity or alkalinity	+	—
Alkalis and alkaline earths	—	⩽1.0%
Appearance of solution	+	—
Acid value of the fatty acids	195–210	—
Appearance of solution of fatty acids	+	—
Arsenic	—	⩽1.5 ppm
Cadmium	⩽5 ppm	—
Lead	⩽25 ppm	⩽0.001%
Chlorides	⩽250 ppm	—
Sulfates	⩽0.6%	—
Organic volatile impurities	—	+
Assay (as Zn)	10.0–12.0%	—
Assay (as ZnO)	—	12.5–14.0%

10 Typical Properties

Autoignition temperature: 421°C
Density: 1.09 g/cm^3
Density (tapped): 0.26 g/cm^3 for standard grade (Durham Chemicals).
Flash point: 277°C
Melting point: 120–122°C
Particle size distribution: 100% through a 44.5-μm sieve (#325 mesh).
Solubility: practically insoluble in ethanol (95%), ether, water, and oxygenated solvents; soluble in acids, benzene, and other aromatic solvents.

11 Stability and Storage Conditions

Zinc stearate is stable and should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Zinc stearate is decomposed by dilute acids.

13 Method of Manufacture

An aqueous solution of zinc sulfate is added to sodium stearate solution to precipitate zinc stearate. The zinc stearate is then washed with water and dried. Zinc stearate may also be prepared from stearic acid and zinc chloride.

14 Safety

Zinc stearate is used in oral and topical pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant excipient. However, following inhalation, it has been associated with fatal pneumonitis, particularly in infants.(1) As a result, zinc stearate has now been removed from baby dusting powders.

LD_{50} (rat, IP): 0.25 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Zinc stearate may be harmful on inhalation and should be used in a well-ventilated environment; a respirator is recommended. In the UK, the long-term (8-hour TWA) occupational exposure limit for zinc stearate is 10 mg/m^3 for total inhalable dust and 4 mg/m^3 for respirable dust. The short-term (15-minutes) exposure limit for total inhalable dust is 20 mg/m^3.(2) In the US, the OSHA limit is 15 mg/m^3 for total dust, 5 mg/m^3 respirable fraction for zinc stearate.(3)

When heated to decomposition, zinc stearate emits acrid smoke and fumes of zinc oxide.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Calcium stearate; magnesium stearate; stearic acid.

18 Comments

The EINECS number for zinc stearate is 209-151-9.

See Magnesium Stearate for further information and references.

19 Specific References

1 Ueda A, Harada K, Ueda T, Nomura S. Experimental study on the pathological changes in lung tissue caused by zinc stearate dust. *Ind Health* 1984; **22**: 243–253.
2 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.
3 JT Baker (2005). Zinc stearate safety data sheet. http://www.jtbaker.com/msds/englishhtml/z4275.htm (accessed 5 April 2005).

20 General References

—

21 Authors

LV Allen.

22 Date of Revision

5 April 2005.

Appendix I: Suppliers Directory

Excipients List

Acacia

UK
A and E Connock (Perfumery and Cosmetics) Ltd
AF Suter and Co Ltd
Colloides Naturels UK Ltd
Courtin & Warner Ltd
JT Baker UK
Paroxite (London) Ltd
Thew, Arnott and Co Ltd

Other European
Alland & Robert
Colloides Naturels International

USA
Colloides Naturels Inc
Delta Distributors Inc
Chart Corp Inc
JT Baker Inc
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
TIC Gums
Voigt Global Distribution LLC

Acesulfame Potassium

UK
Nutrinova UK Ltd

Other European
Nutrinova Nutrition Specialities & Food Ingredients GmbH

USA
Aceto Corp
Nutrinova Inc

Acetic Acid, Glacial

UK
Acetex Chemicals Ltd
Blagden Specialty Chemicals Ltd
BP plc
Eastman Company UK Ltd
Fisher Scientific UK Ltd
JT Baker UK
Peter Whiting (Chemicals) Ltd
Tennants (Distribution) Ltd
Wacker Chemicals Ltd

Other European
Acetex Chimie SA
August Hedinger GmbH & Co
Brenntag AG
Wacker-Chemie GmbH

USA
Ashland
BP Inc
Brenntag Inc
Delta Distributors Inc
Eastman Chemical Co
EM Industries Inc
Fisher Scientific
JT Baker Inc
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America
Vopak USA Inc
Wacker Chemical Corp

Acetone

UK
BP plc
Leading Solvent Supplies Ltd

Other European
Dow Benelux NV
Rohm and Haas Belgium NV

USA
Amresco Inc
Ashland
Dow Chemical Co
Eastman Chemical Co
EMD Chemicals Inc
Penta Manufacturing Co
Sigma-Aldrich Corp
Vopak USA Inc

Acetyltributyl Citrate

UK
Ubichem plc

Other European
Jungbunzlauer

USA
Morflex Inc
Penta Manufacturing Co

Acetyltriethyl Citrate

UK
Ubichem plc

Other European
Jungbunzlauer

USA
Morflex Inc
Penta Manufacturing Co

Agar

UK
Mast Group Ltd
Sigma-Aldrich Company Ltd

USA
Alfa Chem
Amresco Inc
Ashland
EMD Chemicals Inc
Penta Manufacturing Co
TIC Gums
Vopak USA Inc

Albumin

UK
Aarhus United UK Ltd
Paroxite (London) Ltd

Other European
Aarhus United Denmark A/S
Kraeber GmbH & Co

USA
Aarhus United USA Inc
AerChem Inc
Amresco Inc
ZLB Behring
Penta Manufacturing Co
Voigt Global Distribution LLC

Alcohol

UK
Tennants (Distribution) Ltd

Other European
Amylum Ibérica, SA
Brenntag AG

USA
Ashland
Brenntag Inc
Delta Distributors Inc
Dow Chemical Co
Grain Processing Corp

Alginic Acid

UK
Blagden Specialty Chemicals Ltd
Forum Biosciences Ltd
Honeywill & Stein
JRS Pharma Ltd

Other European
FMC Biopolymer
J Rettenmaier & Söhne GmbH and Co

USA
Aceto Corp
FMC Biopolymer
International Specialty Products
JRS Pharma LP
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Voigt Global Distribution LLC

Aliphatic Polyesters

UK
Alfa Chemicals Ltd/Gattefossé UK
Purac Biochem (UK)

Other European
Boehringer Ingelheim GmbH

USA
Boehringer Ingelheim Chemicals Inc
Purac America Inc

Alitame

UK
Danisco Sweeteners Ltd

USA
Danisco USA Inc

Almond Oil

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Aarhus United UK Ltd
Alembic Products Ltd
Paroxite (London) Ltd
Peter Whiting (Chemicals) Ltd
White Sea and Baltic Company Ltd
William Ransom & Son plc

Other European
Aarhus United Denmark A/S

USA
Aarhus United USA Inc
Arista Industries Inc
Charkit Chemical Corp
Chart Corp Inc
Mutchler Inc
Penta Manufacturing Co
Pokonobe Industries Inc
Spectrum Quality Products Inc
Voigt Global Distribution LLC
Welch, Holme & Clark Co Inc

Alpha Tocopherol

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Alembic Products Ltd
Cognis UK Ltd
Cornelius Group plc
Eastman Company UK Ltd
Ubichem plc

Other European
BASF Aktiengesellschaft
Brenntag AG
Cognis Deutschland GmbH
Helm AG

USA
Aceto Corp
Alfa Chem
BASF Corp
Brenntag Inc
Cognis Corp
Eastman Chemical Co
Helm New York Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Takeda Pharmaceuticals North America Inc
Triple Crown America

Others
Takeda Chemical Industries Ltd

Aluminum Hydroxide Adjuvant

UK
Reheis

Other European
Reheis

USA
Reheis Inc

Aluminum Oxide

UK
Pumex (UK) Limited
Fisher Scientific UK Ltd

Other European
Degussa AG

USA
Alfa Chem
EMD Chemicals Inc
Penta Manufacturing Co
Ruger Chemical Co Inc
SPI Pharma Group
Vopak USA Inc

Others
Sumitomo Chemical

Aluminum Phosphate Adjuvant

UK
Reheis

Other European
Reheis

USA
Reheis Inc

Aluminum Stearate

Other European
Magnesia GmbH

USA
Acme-Hardesty
AerChem Inc
Alfa Chem
Ashland
Eastech Chemical Inc
Penta Manufacturing Co
Ruger Chemical Co Inc
Spectrum Quality Products Inc

Ammonia Solution

UK
Tennants (Distribution) Ltd
William Ransom & Son plc

USA
Triple Crown America
Vopak USA Inc

Ammonium Alginate

USA
CP Kelco US Inc

Ascorbic Acid

UK
Fisher Scientific UK Ltd
JT Baker UK
Peter Whiting (Chemicals) Ltd
Raught Ltd
Roche Products Ltd
Tennants (Distribution) Ltd
Thew, Arnott and Co Ltd

Other European
BASF Aktiengesellschaft
Brenntag AG
Helm AG

USA
Aceto Corp
AerChem Inc
Alfa Chem
Amresco Inc
Barrington Chemical Corp
BASF Corp
Brenntag Inc
Charkit Chemical Corp
Charles Bowman & Co
Delta Distributors Inc
EM Industries Inc
Fisher Scientific
George Uhe Co Inc
Hawkins Chemical Inc
Helm New York Inc
JT Baker Inc
Kraft Chemical Co
Mutchler Inc
Particle Dynamics Inc
Penta Manufacturing Co
Seltzer Chemicals Inc
Spectrum Quality Products Inc
Takeda Pharmaceuticals North America Inc
Triple Crown America
Voigt Global Distribution LLC
Vopak USA Inc

Others
Shijiazhuang Pharmaceutical Group Co Ltd
Takeda Pharmaceutical Company Ltd

Ascorbyl Palmitate

UK
Roche Products Ltd

Other European
BASF Aktiengesellschaft

USA
Aceto Corp
BASF Corp
Delta Distributors Inc
EM Industries Inc
George Uhe Co Inc
Hawkins Chemical Inc
Helm New York Inc
Penta Manufacturing Co
RIA International
Spectrum Quality Products Inc
Voigt Global Distribution LLC

Others
Xinchem Co

Aspartame

UK
Blagden Specialty Chemicals Ltd
DSM UK Ltd
Tennants (Distribution) Ltd

Other European
Ajinomoto Switzerland AG
Brenntag AG
DSM Fine Chemicals
Helm AG

USA
Aceto Corp
AerChem Inc
Ashland
Brenntag Inc
Delta Distributors Inc
DSM Fine Chemicals Inc
Hawkins Chemical Inc
Helm New York Inc
Merisant
Spectrum Quality Products Inc
Triple Crown America
Voigt Global Distribution LLC
Vopak USA Inc

Others
LS Raw Materials Ltd
Xinchem Co

Bentonite

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Paroxite (London) Ltd
Raught Ltd
Tennants (Distribution) Ltd
Thew, Arnott and Co Ltd
Wilfrid Smith Ltd

USA
American Colloid Co
Charles B Chrystal Co Inc
Farma International Inc
Kraft Chemical Co
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Whittaker Clark, and Daniels Inc

Benzalkonium Chloride

UK
Raught Ltd
Tennants (Distribution) Ltd
Ubichem plc

Other European
Brenntag AG
FeF Chemicals A/S

USA
AerChem Inc
Alfa Chem
Brenntag Inc
EM Industries Inc
Penta Manufacturing Co
RIA International
Sanofi-Synthelabo Inc
Spectrum Quality Products Inc
Triple Crown America

Others
Yee Young Cerachem Ltd

Benzethonium Chloride

UK
Lonza UK Ltd

Other European
Lonza Ltd

USA
Penta Manufacturing Co
Spectrum Quality Products Inc

Benzoic Acid

UK
Ashland
Clariant UK Ltd
Cornelius Group plc
Courtin & Warner Ltd
Dow Chemical Company (UK)
DSM UK Ltd
Fisher Scientific UK Ltd
JT Baker UK
Raught Ltd
Sparkford Chemicals Ltd
Tennants (Distribution) Ltd
Ubichem plc

Other European
Brenntag AG
DSM Fine Chemicals
Haltermann GmbH

USA
Aceto Corp
AerChem Inc
Amresco Inc
Brenntag Inc
Charkit Chemical Corp
DSM Fine Chemicals Inc
EM Industries Inc
Fisher Scientific
JT Baker Inc
Mutchler Inc
Napp Technologies Inc
Nipa Laboratories Inc
Penta Manufacturing Co
RIA International
Spectrum Quality Products Inc
Triple Crown America
Voigt Global Distribution LLC
Vopak USA Inc

Others
LS Raw Materials Ltd
San Fu Chemical Company Ltd

Benzyl Alcohol

UK
DSM UK Ltd
Fisher Scientific UK Ltd
Haarmann & Reimer Ltd
JT Baker UK
Raught Ltd
Tennants (Distribution) Ltd
Ubichem plc

Other European
Brenntag AG
Chemco France
DSM Fine Chemicals
Haarmann & Reimer GmbH
Tessenderlo Chemie

USA
AerChem Inc
Brenntag Inc
Charkit Chemical Corp
DSM Fine Chemicals Inc
EM Industries Inc
Fisher Scientific
Hawkins Chemical Inc
JT Baker Inc
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Voigt Global Distribution LLC
Vopak USA Inc

Others
LS Raw Materials Ltd

Benzyl Benzoate

UK
Dow Chemical Company (UK)
Haarmann & Reimer Ltd
Raught Ltd
William Ransom & Son plc

Other European
Haarmann & Reimer GmbH
Haltermann GmbH
Helm AG

USA
Helm New York Inc
Morflex Inc
Mutchler Inc
Penta Manufacturing Co
Reilly Industries Inc
Spectrum Quality Products Inc
Voigt Global Distribution LLC

Others
LS Raw Materials Ltd

Bronopol

UK
Honeywill & Stein
Raught Ltd
Tennants (Distribution) Ltd

Other European
BASF Aktiengesellschaft

USA
BASF Corp
Inolex Chemical Co
Spectrum Quality Products Inc

Others
Cosmos Chemical Co Ltd
LS Raw Materials Ltd

Butylated Hydroxyanisole

UK
Eastman Company UK Ltd
Honeywill & Stein
Sparkford Chemicals Ltd

Other European
Brenntag AG

USA
Aceto Corp
Ashland
Brenntag Inc
Delta Distributors Inc
Eastman Chemical Co
Kraft Chemical Co
Penta Manufacturing Co
Spectrum Quality Products Inc
Voigt Global Distribution LLC

Others
LS Raw Materials Ltd

Butylated Hydroxytoluene

UK
Eastman Company UK Ltd
Honeywill & Stein
Raught Ltd
Sparkford Chemicals Ltd

Other European
Brenntag AG
Helm AG

USA
Aceto Corp
Alfa Chem
Ashland
Brenntag Inc
Delta Distributors Inc
Eastman Chemical Co
Helm New York Inc
Kraft Chemical Co
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Voigt Global Distribution LLC

Others
LS Raw Materials Ltd

Butylparaben

UK
Clariant UK Ltd
JT Baker UK

Other European
Chemag Aktiengesellschaft
Induchem AG

USA
JT Baker Inc
Lipo Chemicals Inc
Napp Technologies Inc
Nipa Laboratories Inc
Penta Manufacturing Co
Protameen Chemicals
Spectrum Quality Products Inc
Voigt Global Distribution LLC
Vopak USA Inc

Calcium Carbonate

UK
Blagden Specialty Chemicals Ltd
DMV UK
Fisher Scientific UK Ltd
Forum Biosciences Ltd
JT Baker UK
Paroxite (London) Ltd
Peter Whiting (Chemicals) Ltd
Tennants (Distribution) Ltd
Thew, Arnott and Co Ltd

Other European
August Hedinger GmbH & Co
Brenntag AG
DMV Pharma
Dr Paul Lohmann GmbH KG
J Rettenmaier & Söhne GmbH and Co
Lehmann & Voss & Co
Magnesia GmbH
Schaefer Kalk KG

USA
Aceto Corp
AerChem Inc
Barrington Chemical Corp
Brenntag Inc
Charles B Chrystal Co Inc
Delta Distributors Inc
EM Industries Inc
EM Sergeant Pulp & Chemical Co Inc
Fisher Scientific
Generichem Corp
Hawkins Chemical Inc
JT Baker Inc
Mutchler Inc
Particle Dynamics Inc
Penta Manufacturing Co
RIA International
Spectrum Quality Products Inc
SPI Pharma Group
Triple Crown America
Voigt Global Distribution LLC
Vopak USA Inc
Whittaker Clark, and Daniels Inc

Calcium Phosphate, Dibasic Anhydrous

UK
Forum Biosciences Ltd
JRS Pharma Ltd
Peter Whiting (Chemicals) Ltd
Raught Ltd
Rhodia Organic Fine Ltd

Other European
Brenntag AG

USA
Brenntag Inc
Charkit Chemical Corp
Fuji Chemical Industries Health Science (USA) Inc
Gallard-Schlesinger Industries
JRS Pharma LP
Mutchler Inc
Penta Manufacturing Co
Rhodia Pharma Solutions Inc
Spectrum Quality Products Inc
Triple Crown America

Others
Fuji Chemical Industry Co Ltd

Calcium Phosphate, Dibasic Dihydrate

UK
Fisher Scientific UK Ltd
Forum Biosciences Ltd
JRS Pharma Ltd
Peter Whiting (Chemicals) Ltd
Raught Ltd
Rhodia Organic Fine Ltd

Other European
Brenntag AG

USA
Aceto Corp
Brenntag Inc
Fisher Scientific
Gallard-Schlesinger Industries
JRS Pharma LP
Mutchler Inc
Penta Manufacturing Co
Rhodia Pharma Solutions Inc
Spectrum Quality Products Inc
Triple Crown America

Calcium Phosphate, Tribasic

UK
Fisher Scientific UK Ltd
Peter Whiting (Chemicals) Ltd
Raught Ltd
Rhodia Organic Fine Ltd

Other European
Brenntag AG
Brenntag NV

USA
Brenntag Inc
Fisher Scientific
Gallard-Schlesinger Industries
Penta Manufacturing Co
Rhodia Pharma Solutions Inc
Spectrum Quality Products Inc
Triple Crown America

Calcium Stearate

UK
Allchem Pharma
James M Brown Ltd
Paroxite (London) Ltd
Raught Ltd
Tennants (Distribution) Ltd

Other European
Brenntag AG
Dr Paul Lohmann GmbH KG
Magnesia GmbH

USA
Aceto Corp
AerChem Inc
Alfa Chem
Ashland
Brenntag Inc
Charkit Chemical Corp
Kraft Chemical Co
JT Baker Inc
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America
Voigt Global Distribution LLC
Vopak USA Inc
Whittaker Clark, and Daniels Inc

Calcium Sulfate

UK
Forum Biosciences Ltd
JRS Pharma Ltd
Paroxite (London) Ltd
Peter Whiting (Chemicals) Ltd

Other European
Dr Paul Lohmann GmbH KG

USA
AerChem Inc
Charles B Chrystal Co Inc
JRS Pharma LP
Particle Dynamics Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America
Voigt Global Distribution LLC
Vopak USA Inc
Whittaker Clark, and Daniels Inc

Canola Oil

UK
Aarhus United UK Ltd
Adina Chemicals Ltd
Karlshamns Ltd

Other European
Aarhus United Denmark A/S
Karlshamns AB

USA
Aarhus United USA Inc
Arista Industries Inc
Charkit Chemical Corp
Lipo Chemicals Inc
Penta Manufacturing Co
Pokonobe Industries Inc
Welch, Holme & Clark Co Inc

Carbomer

UK
Goldschmidt UK Ltd

USA
Noveon Inc
Rita Corp
Spectrum Quality Products Inc

Carbon Dioxide

UK
Air Liquide UK Ltd
Air Products (Gases) plc
BOC Gases

USA
Air Liquide America Corp
BOC Gases

Carboxymethylcellulose Calcium

USA
Aceto Corp
Ashland
Kraft Chemical Co

Carboxymethylcellulose Sodium

UK
Hercules Ltd
Honeywill & Stein

Other European
Akzo Nobel Functional Chemicals bv
Brenntag AG
Lehmann & Voss & Co
Noviant

USA
Aqualon
Ashland
Brenntag Inc
Delta Distributors Inc
FMC Biopolymer
Kraft Chemical Co
Spectrum Quality Products Inc
Whittaker Clark, and Daniels Inc

Carrageenan

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Paroxite (London) Ltd
Thew, Arnott and Co Ltd

Other European
Brenntag AG
FMC Biopolymer
Lehmann & Voss & Co

USA
Aqualon
Ashland
Brenntag Inc
Charkit Chemical Corp
Delta Distributors Inc
FMC Biopolymer
Spectrum Quality Products Inc
TIC Gums
Voigt Global Distribution LLC

Castor Oil

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Adina Chemicals Ltd
Alembic Products Ltd
Blagden Speciality Chemicals Ltd
Corcoran Chemicals Ltd
Croda Chemicals Ltd
Fisher Scientific UK Ltd
JT Baker UK
Kimpton Brothers Ltd
Paroxite (London) Ltd
White Sea and Baltic Company Ltd
William Ransom & Son plc
WS Lloyd Ltd

USA
Acme-Hardesty
Arista Industries Inc
Avatar Corp
Charkit Chemical Corp
Croda Inc
Fisher Scientific
JT Baker Inc
Lipo Chemicals Inc
Mutchler Inc
Paddock Laboratories Inc
Penta Manufacturing Co
Pokonobe Industries Inc
Spectrum Quality Products Inc
Triple Crown America
Voigt Global Distribution LLC
Vopak USA Inc
Welch, Holme & Clark Co Inc

Castor Oil, Hydrogenated

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Cognis UK Ltd
Cornelius Group plc
Croda Chemicals Ltd
Goldschmidt UK Ltd
Paroxite (London) Ltd
White Sea and Baltic Company Ltd

Other European
Arion & Delahaye
Cognis Deutschland GmbH

USA
ABITEC Corp
Cognis Corp
Croda Inc
GR O'Shea Company

Cellulose, Microcrystalline

UK
Allchem Pharma
Cornelius Group plc
DMV UK
Forum Biosciences Ltd
Honeywill & Stein
ISP Europe
JRS Pharma Ltd

Other European
DMV Pharma
FMC Biopolymer
Helm AG
J Rettenmaier & Söhne GmbH and Co
Lehmann & Voss & Co
NP Pharm

USA
Alfa Chem
Ashland
Barrington Chemical Corp
Delta Distributors Inc
FMC Biopolymer
Helm New York Inc
International Specialty Products
JRS Pharma LP
Mutchler Inc
Spectrum Quality Products Inc
Voigt Global Distribution LLC

Others
Aastrid International
Asahi Kasei Corporation
Glide Chem Pvt Ltd
LS Raw Materials Ltd

Cellulose, Powdered

UK
Allchem Pharma

Other European
CFF GmbH and Co KG
J Rettenmaier & Söhne GmbH and Co

USA
Alfa Chem
International Fiber Corporation
Mutchler Inc
Triple Crown America
Voigt Global Distribution LLC

Cellulose, Silicified Microcrystalline

UK
JRS Pharma Ltd

Other European
J Rettenmaier & Söhne GmbH and Co

USA
JRS Pharma LP

Cellulose Acetate

UK
Eastman Company UK Ltd
Honeywill & Stein
Eastman Chemical Co

Cellulose Acetate Phthalate

UK
Eastman Company UK Ltd
Honeywill & Stein
Raught Ltd

Other European
FMC Biopolymer
Lehmann & Voss & Co

USA
Eastman Chemical Co
FMC Biopolymer

Ceratonia

UK
Rhodia Organic Fine Ltd

Other European
Brenntag AG

USA
Ashland
Brenntag Inc
Rhodia Pharma Solutions Inc
TIC Gums

Cetostearyl Alcohol

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Cognis UK Ltd
Croda Chemicals Ltd
Efkay Chemicals Ltd
Goldschmidt UK Ltd
H Foster & Co (Stearines) Ltd
Raught Ltd
White Sea and Baltic Company Ltd

Other European
BASF Aktiengesellschaft
Cognis Deutschland GmbH

USA
Avatar Corp
BASF Corp
Cognis Corp
Croda Inc
Penta Manufacturing Co
Rita Corp
Spectrum Quality Products Inc

Others
LS Raw Materials Ltd

Cetrimide

UK
Cornelius Group plc
Raught Ltd

Other European
FeF Chemicals A/S

USA
Aceto Corp
Alfa Chem
Triple Crown America

Others
LS Raw Materials Ltd

Cetyl Alcohol

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Aarhus United UK Ltd
Adina Chemicals Ltd
Cognis UK Ltd
Croda Chemicals Ltd
Efkay Chemicals Ltd
Goldschmidt UK Ltd
Kimpton Brothers Ltd
Raught Ltd
White Sea and Baltic Company Ltd

Other European
Aarhus United Denmark A/S
Brenntag AG
Cognis Deutschland GmbH

USA
Aarhus United USA Inc
Avatar Corp
Brenntag Inc
Cognis Corp
Croda Inc
Hawkins Chemical Inc
Kraft Chemical Co
Lipo Chemicals Inc
M Michel and Company Inc
Mutchler Inc
Penta Manufacturing Co
Protameen Chemicals
Rita Corp
Spectrum Quality Products Inc
Stepan Co
Vopak USA Inc

Others
LS Raw Materials Ltd

Cetylpyridinium Chloride

USA
Aceto Corp

Chitosan

UK
FMC Biopolymer

USA
FMC Biopolymer
Seltzer Chemicals Inc

Chlorhexidine

UK
Raught Ltd

USA
George Uhe Co Inc
Napp Technologies Inc

Others
LS Raw Materials Ltd

Chlorobutanol

UK
Blagden Specialty Chemicals Ltd
Courtin & Warner Ltd
Raught Ltd

USA
Penta Manufacturing Co
Spectrum Quality Products Inc

Others
LS Raw Materials Ltd

Chlorocresol

UK
Raught Ltd

Others
LS Raw Materials Ltd

Chlorodifluoroethane (HCFC)

UK
Allchem Pharma

Other European
DuPont de Nemours Int'l SA
Solvay Fluor GmbH

USA
DuPont

Chloroxylenol

UK
Coventry Chemicals Ltd
Raught Ltd

USA
Nipa Laboratories Inc
Spectrum Quality Products Inc

Cholesterol

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Croda Chemicals Ltd
JT Baker UK
Paroxite (London) Ltd
Ubichem plc

USA
Aceto Corp
Amresco Inc
Avanti Polar Lipids Inc
Charles Bowman & Co
Croda Inc
EM Industries Inc
JT Baker Inc
Penta Manufacturing Co
Rita Corp
Spectrum Quality Products Inc
Voigt Global Distribution LLC

Citric Acid Monohydrate

UK
Blagden Specialty Chemicals Ltd
Cerestar UK Ltd
Courtin & Warner Ltd
Fisher Scientific UK Ltd
JT Baker UK
Peter Whiting (Chemicals) Ltd
Raught Ltd
Roche Products Ltd
Tate and Lyle plc
Tennants (Distribution) Ltd
Thew, Arnott and Co Ltd
Ubichem plc

Other European
Arion & Delahaye
Brenntag AG
Cerestar International
Dr Paul Lohmann GmbH KG
Jungbunzlauer

USA
Aceto Corp
Amresco Inc
Ashland
Avatar Corp
Brenntag Inc
Charkit Chemical Corp
Delta Distributors Inc
EM Industries Inc
EM Sergeant Pulp & Chemical Co Inc
Fisher Scientific
George Uhe Co Inc
Hawkins Chemical Inc
JT Baker Inc
Kraft Chemical Co
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America
Voigt Global Distribution LLC
Vopak USA Inc

Others
LS Raw Materials Ltd

Colloidal Silicon Dioxide

UK
Degussa Ltd
Grace Davison
Wacker Chemicals Ltd

Other European
Biesterfeld Spezialchemie GmbH
Brenntag AG
Cabot GmbH
Degussa AG
Wacker-Chemie GmbH

USA
Brenntag Inc
Cabot Corp
Degussa Corp
Mutchler Inc
Vopak USA Inc
Wacker Chemical Corp

Coloring Agents

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Colorcon Ltd
DMV UK
Thew, Arnott and Co Ltd

Other European
DMV Pharma

USA
Ashland
Colorcon
Triple Crown America
Warner Jenkinson Pharmaceutical
Whittaker Clark, and Daniels Inc

Copovidone

UK
BASF Plc

Other European
ISP Europe
BASF Aktiengesellschaft

USA
BASF Corp
International Specialty Products

Corn Oil

UK
Aarhus United UK Ltd
Alembic Products Ltd
Cerestar UK Ltd
Cognis UK Ltd
Efkay Chemicals Ltd
Karlshamns Ltd

Other European
Aarhus United Denmark A/S
Cerestar International
Cognis Deutschland GmbH
Karlshamns AB

USA
Aarhus United USA Inc
Arista Industries Inc
Avatar Corp
Cargill Corp
Charkit Chemical Corp
Cognis Corp
Grain Processing Corp
Penta Manufacturing Co
Pokonobe Industries Inc
Spectrum Quality Products Inc
Welch, Holme & Clark Co Inc

Cottonseed Oil

UK
Blagden Specialty Chemicals Ltd
Fisher Scientific UK Ltd
Karlshamns Ltd

Other European
Karlshamns AB

USA
Arista Industries Inc
Charkit Chemical Corp
Fisher Scientific
Hawkins Chemical Inc
Mutchler Inc
Penta Manufacturing Co
Pokonobe Industries Inc
Spectrum Quality Products Inc
Welch, Holme & Clark Co Inc

Cresol

USA
Amresco Inc
Penta Manufacturing Co
PMC Specialities Group Inc
Spectrum Quality Products Inc

Croscarmellose Sodium

UK
Allchem Pharma
Avebe UK Ltd
DMV UK
Honeywill & Stein

Other European
Akzo Nobel Functional Chemicals bv
Avebe Group
DMV Pharma
FMC Biopolymer
J Rettenmaier & Söhne GmbH and Co
Lehmann & Voss & Co

USA
Avebe America Inc
FMC Biopolymer
Generichem Corp
Mutchler Inc
RIA International
Spectrum Quality Products Inc
Voigt Global Distribution LLC

Crospovidone

UK
BASF Plc
Blagden Specialty Chemicals Ltd
ISP Europe

Other European
August Hedinger GmbH & Co
BASF Aktiengesellschaft

USA
BASF Corp
International Specialty Products

Cyclodextrins

UK
Cerestar UK Ltd
Pfanstiehl (Europe) Ltd
Roquette (UK) Ltd
Wacker Chemicals Ltd

Other European
Cerestar International
Roquette Frères
Wacker-Chemie GmbH

USA
Cargill Corp
CTD Inc
Ferro Pfanstiehl Laboratories Inc
Research Diagnostics Inc
Roquette America Inc
Spectrum Quality Products Inc
Voigt Global Distribution LLC
Wacker Chemical Corp

Cyclomethicone

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Dow Corning

USA
Dow Corning

Denatonium Benzoate

UK
A and E Connock (Perfumery and Cosmetics) Ltd

USA
Barrington Chemical Corp
Burlington Bio-medical and Scientific Corp
Chart Corp Inc

Others
Fine Chemicals Corporation (Pty) Ltd

Dextrates

UK
Forum Biosciences Ltd
JRS Pharma Ltd

Other European
J Rettenmaier & Söhne GmbH and Co
JRS Pharma LP

USA
Spectrum Quality Products Inc

Dextrin

UK
Avebe UK Ltd
Roquette (UK) Ltd
Tennants (Distribution) Ltd

Other European
Avebe Group

USA
Avebe America Inc
Generichem Corp
Mutchler Inc
Roquette Frères
Vopak USA Inc

Dextrose

UK
Cerestar UK Ltd
Corcoran Chemicals Ltd
Fisher Scientific UK Ltd
Forum Biosciences Ltd
JT Baker UK
Pfanstiehl (Europe) Ltd
Raught Ltd
Roquette (UK) Ltd

Other European
Biesterfeld Spezialchemie GmbH
Brenntag AG
Cerestar International
Helm AG
Roquette Frères

USA
Ashland
Brenntag Inc
Cargill Corp
Delta Distributors Inc
EM Sergeant Pulp & Chemical Co Inc
Fisher Scientific
Helm New York Inc
JT Baker Inc
Mutchler Inc
Penta Manufacturing Co
Ferro Pfanstiehl Laboratories Inc
Roquette America Inc
Spectrum Quality Products Inc
Voigt Global Distribution LLC
Vopak USA Inc

Others
LS Raw Materials Ltd

Dibutyl Sebacate

UK
A and E Connock (Perfumery and Cosmetics) Ltd

USA
Aceto Corp
Morflex Inc
Penta Manufacturing Co
Reilly Industries Inc
Sigma-Aldrich Corp

Diethanolamine

UK
Sasol UK Ltd
Tennants (Distribution) Ltd
Ubichem plc

Other European
Brenntag AG

USA
Amresco Inc
Brenntag Inc
Sasol North America Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America
Vopak USA Inc

Diethyl Phthalate

UK
BASF Plc
Eastman Company UK Ltd

Other European
BASF Aktiengesellschaft
Brenntag AG

USA
BASF Corp
Brenntag Inc
Eastman Chemical Co
Penta Manufacturing Co
Spectrum Quality Products Inc
Vopak USA Inc

Difluoroethane (HFC)

Other European
DuPont de Nemours Int'l SA
Solvay Fluor GmbH

USA
Aeropres Corp

Dimethicone

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Dow Corning
Goldschmidt UK Ltd
Honeywill & Stein
Raught Ltd

Other European
Biesterfeld Spezialchemie GmbH

USA
Crompton Corp
Dow Corning

Dimethyl Ether

UK
Air Liquide UK Ltd

Other European
DuPont de Nemours Int'l SA

USA
Aeropres Corp

Dimethyl Sulfoxide

USA
Spectrum Quality Products Inc

Dimethylacetamide

UK
BASF Plc
JT Baker UK
Sigma-Aldrich Company Ltd

Other European
BASF Aktiengesellschaft
DuPont de Nemours Int'l SA

USA
DuPont
Spectrum Quality Products Inc

Docusate Sodium

USA
Penta Manufacturing Co
Spectrum Quality Products Inc

Edetic Acid

Other European
Akzo Nobel Functional Chemicals bv

USA
Brenntag Inc
Dow Chemical Co
Spectrum Quality Products Inc

Erythorbic Acid

USA
Biddle Sawyer Corp
Brainerd Chemical Company Inc
Premium Ingredients Ltd
Seidler Chemical Company
Zhong Ya Chemical (USA) Ltd

Others
Univar Canada Ltd
Wintersun Chemical

Erythritol

UK
Cerestar UK Ltd

Other European
Cerestar International

USA
Cargill Corp

Others
Mitsubishi-Kagaku Foods Corporation

Ethyl Acetate

UK
BP plc
Corcoran Chemicals Ltd
Eastman Company UK Ltd
Fisher Scientific UK Ltd
Raught Ltd
Tennants (Distribution) Ltd

Other European
August Hedinger GmbH & Co

USA
BP Inc
AerChem Inc
Dow Chemical Co
Eastman Chemical Co
Fisher Scientific
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America

Others
Aastrid International

Ethyl Maltol

Other European
Helm AG

USA
Helm New York Inc
Penta Manufacturing Co

Ethyl Oleate

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Croda Chemicals Ltd

USA
Croda Inc
Penta Manufacturing Co
Spectrum Quality Products Inc

Ethyl Vanillin

UK
Blagden Specialty Chemicals Ltd
Courtin & Warner Ltd

Other European
Brenntag AG
Helm AG

USA
AerChem Inc
Ashland
Brenntag Inc
Chart Corp Inc
Delta Distributors Inc
Helm New York Inc
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Voigt Global Distribution LLC
Vopak USA Inc

Ethylcellulose

UK
Hercules Ltd
Honeywill & Stein

Other European
FMC Biopolymer

USA
Aqualon
Dow Chemical Co
FMC Biopolymer
Mutchler Inc
Spectrum Quality Products Inc
Vopak USA Inc

Others
Glide Chem Pvt Ltd

Ethylene Vinyl Acetate

UK
3M United Kingdom Plc

USA
3M Drug Delivery Systems

Ethylparaben

UK
Clariant UK Ltd

Other European
Brenntag AG
Chemag Aktiengesellschaft
Induchem AG

USA
Brenntag Inc
Lipo Chemicals Inc
Napp Technologies Inc
Nipa Laboratories Inc
Penta Manufacturing Co
Protameen Chemicals
Spectrum Quality Products Inc
Vopak USA Inc

Fructose

UK
Cerestar UK Ltd
Corcoran Chemicals Ltd
Danisco Sweeteners Ltd
Fisher Scientific UK Ltd
Forum Biosciences Ltd
Pfanstiehl (Europe) Ltd

Other European
Amylum Ibérica, SA
Brenntag AG
Cerestar International

USA
Aceto Corp
Tate & Lyle
Alfa Chem
Amresco Inc
Ashland
Barrington Chemical Corp
Brenntag Inc
Cargill Corp
Danisco USA Inc
EM Industries Inc
Fisher Scientific
Penta Manufacturing Co
Ferro Pfanstiehl Laboratories Inc
Spectrum Quality Products Inc
SPI Pharma Group
Voigt Global Distribution LLC

Others
LS Raw Materials Ltd

Fumaric Acid

UK
DSM UK Ltd
Lonza UK Ltd
Peter Whiting (Chemicals) Ltd
Raught Ltd
Sparkford Chemicals Ltd

Other European
Brenntag AG
DSM Fine Chemicals
Helm AG
Lonza Ltd

USA
Aceto Corp
Tate & Lyle
Alfa Chem
Ashland
Brenntag Inc
DSM Fine Chemicals Inc
Gallard-Schlesinger Industries
Helm New York Inc
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Takeda Pharmaceuticals North America Inc
Triple Crown America
Vopak USA Inc

Others
Aastrid International
Takeda Pharmaceutical Company Ltd

Gelatin

UK
Corcoran Chemicals Ltd
Croda Chemicals Ltd
Global Ceramic Materials Ltd
JT Baker UK
Paroxite (London) Ltd
PB Gelatins UK Ltd
Thew, Arnott and Co Ltd

Other European
Gelatine Smits Beheer BV
PB Gelatins Belgium

USA
Ashland
Gallard-Schlesinger Industries
JT Baker Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America

Glucose, Liquid

UK
Cerestar UK Ltd
Courtin & Warner Ltd
Roquette (UK) Ltd

Other European
Amylum Ibérica, SA
Cerestar International
Roquette Frères

USA
Cargill Corp
Delta Distributors Inc
Penta Manufacturing Co
Roquette America Inc

Glycerin

UK
Cognis UK Ltd
Corcoran Chemicals Ltd
Courtin & Warner Ltd
Croda Chemicals Ltd
Efkay Chemicals Ltd
Fisher Scientific UK Ltd
H Foster & Co (Stearines) Ltd
JT Baker UK
Karlshamns Ltd
Kimpton Brothers Ltd
Lonza UK Ltd
Raught Ltd
Stan Chem International Ltd
Tennants (Distribution) Ltd
Uniqema
White Sea and Baltic Company Ltd
William Ransom & Son plc

Other European
August Hedinger GmbH & Co
Brenntag AG
Cognis Deutschland GmbH
Karlshamns AB
Lonza Ltd

USA
Alfa Chem
Ashland
Avatar Corp
Brenntag Inc
Cognis Corp
Delta Distributors Inc
Dow Chemical Co
Fisher Scientific
JT Baker Inc
Kraft Chemical Co
Penta Manufacturing Co
Protameen Chemicals
Rita Corp
Spectrum Quality Products Inc
Triple Crown America
Voigt Global Distribution LLC
Vopak USA Inc
Welch, Holme & Clark Co Inc

Others
Gadot Petrochemical Industries Ltd

Glyceryl Behenate

UK
Alfa Chemicals Ltd/Gattefossé UK

Other European
Gattefossé s.a.

USA
Gattefossé Corp

Glyceryl Monooleate

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Alfa Chemicals Ltd/Gattefossé UK
Cognis UK Ltd
Croda Chemicals Ltd
Goldschmidt UK Ltd
Honeywill & Stein
Lonza UK Ltd

Other European
Cognis Deutschland GmbH
Gattefossé s.a.
Lonza Ltd

USA
ABITEC Corp
Cognis Corp
Croda Inc
Penta Manufacturing Co
Gattefossé Corp
Stepan Co
Vopak USA Inc

Glyceryl Monostearate

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Alfa Chemicals Ltd
Cognis UK Ltd
Corcoran Chemicals Ltd
Croda Chemicals Ltd
Goldschmidt UK Ltd
H Foster & Co (Stearines) Ltd
Honeywill & Stein
Lonza UK Ltd
Sasol UK Ltd

Other European
Cognis Deutschland GmbH
Gattefossé s.a.
Lonza Ltd

USA
ABITEC Corp
Sasol North America Inc
Cognis Corp
Croda Inc

Delta Distributors Inc
Gattefossé Corp
Lipo Chemicals Inc
Mutchler Inc
Penta Manufacturing Co
Protameen Chemicals
Rita Corp
Stepan Co
Vopak USA Inc

Others
LS Raw Materials Ltd

Glyceryl Palmitostearate

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Alfa Chemicals Ltd/Gattefossé UK

Other European
Gattefossé s.a.

USA
Gattefossé Corp

Guar Gum

UK
AF Suter and Co Ltd
Corcoran Chemicals Ltd
Rhodia Organic Fine Ltd
Stan Chem International Ltd
Thew, Arnott and Co Ltd

Other European
Brenntag AG
Helm AG

USA
Aqualon
Ashland
Barrington Chemical Corp
Brenntag Inc
Charkit Chemical Corp
Chart Corp Inc
Delta Distributors Inc
Helm New York Inc
Penta Manufacturing Co
Rhodia Pharma Solutions Inc
Spectrum Quality Products Inc
TIC Gums
Triple Crown America
Voigt Global Distribution LLC
Vopak USA Inc

Others
LS Raw Materials Ltd

Hectorite

USA
Rennecker Ltd

Heptafluoropropane (HFC)

Other European
DuPont de Nemours Int’l SA

Hydrocarbons (HC)

UK
Air Products (Gases) plc
Tennants (Distribution) Ltd

Other European
Chevron Texaco Global Lubricants Benelux

Hydrochloric Acid

UK
JT Baker UK
Tennants (Distribution) Ltd

Other European
Brenntag AG

USA
AerChem Inc
Ashland
Brenntag Inc
Delta Distributors Inc
EM Industries Inc
JT Baker Inc
Spectrum Quality Products Inc
Triple Crown America
Vopak USA Inc

Hydroxyethyl Cellulose

UK
Clariant UK Ltd
Hercules Ltd
Honeywill & Stein
Paroxite (London) Ltd

USA
Aqualon
Clariant Corp
Delta Distributors Inc
Dow Chemical Co
Spectrum Quality Products Inc
Voigt Global Distribution LLC

Hydroxyethylmethyl Cellulose

UK
Clariant UK Ltd
Hercules Ltd

USA
Aqualon
Clariant Corp

Hydroxypropyl Cellulose

UK
Hercules Ltd
Honeywill & Stein

Other European
Nippon Soda Co Ltd

USA
Aqualon
Nippon Soda Co Ltd
Spectrum Quality Products Inc
Voigt Global Distribution LLC

Others
Nippon Soda Co Ltd

Hydroxypropyl Cellulose, Low-substituted

UK
RW Unwin & Co Ltd

USA
Biddle Sawyer Corp
Voigt Global Distribution LLC

Others
Shin-Etsu Chemical Co Ltd

Hydroxypropyl Starch

UK
Tate & Lyle plc
Cerestar UK Ltd

USA
Lipscomb Chemical Company Inc

Hypromellose

UK
Clariant UK Ltd
Colorcon Ltd
RW Unwin & Co Ltd
Ubichem plc

USA
Ashland
Biddle Sawyer Corp
Clariant Corp
Colorcon
Cornelius Group plc
Dow Chemical Co
Hawkins Chemical Inc
Spectrum Quality Products Inc
Warner Jenkinson Pharmaceutical
Vopak USA Inc

Others
Glide Chem Pvt Ltd
Shin-Etsu Chemical Co Ltd

Hypromellose Acetate Succinate

UK
RW Unwin & Co Ltd

Others
Shin-Etsu Chemical Co Ltd

Hypromellose Phthalate

UK
RW Unwin & Co Ltd
Ubichem plc

USA
Biddle Sawyer Corp

Others
Shin-Etsu Chemical Co Ltd

Imidurea

UK
ISP Europe

USA
International Specialty Products
Protameen Chemicals
Spectrum Quality Products Inc

Inulin

Other European
Orafti
Palatinit GmbH
Sensus

USA
Sensus America LLC
TIC Gums

Iron Oxides

UK
Lanxess Ltd
PMC Chemicals Ltd

USA
Reade Advanced Materials Inc
Lanxess Corp

Isomalt

Other European
Cargill Cerestar BVBA
Palatinit GmbH

USA
Cargill Corp

Others
Cerestar Jiliang Maize Industry Co Ltd

Isopropyl Alcohol

UK
Honeywill & Stein
JT Baker UK
Sasol UK Ltd
Tennants (Distribution) Ltd
William Ransom & Son plc

Other European
August Hedinger GmbH & Co
Brenntag AG
Sasol Germany GmbH

USA
Amresco Inc
Brenntag Inc
Delta Distributors Inc
Dow Chemical Co
JT Baker Inc
Penta Manufacturing Co
Sasol North America Inc
Spectrum Quality Products Inc
Triple Crown America
Vopak USA Inc

Isopropyl Myristate

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Adina Chemicals Ltd
Cognis UK Ltd
Corcoran Chemicals Ltd
Croda Chemicals Ltd
Dow Chemical Company (UK)
Goldschmidt UK Ltd
Paroxite (London) Ltd
Uniqema

Other European
Brenntag AG
Cognis Deutschland GmbH
Haltermann GmbH

USA
Akzo Nobel Inc
Brenntag Inc
Cognis Corp
Croda Inc
Delta Distributors Inc
Inolex Chemical Co
Kraft Chemical Co
Lipo Chemicals Inc
Penta Manufacturing Co
Rita Corp
Spectrum Quality Products Inc
Stepan Co

Others
LS Raw Materials Ltd

Isopropyl Palmitate

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Adina Chemicals Ltd
Cognis UK Ltd
Croda Chemicals Ltd
Dow Chemical Company (UK)
Goldschmidt UK Ltd
Paroxite (London) Ltd

Other European
Brenntag AG
Cognis Deutschland GmbH
Haltermann GmbH

USA
Alzo International Inc
Brenntag Inc
Cognis Corp
Croda Inc
Eastech Chemical Inc
Inolex Chemical Co
Kraft Chemical Co
Lipo Chemicals Inc
Penta Manufacturing Co
Noveon Inc
Protameen Chemicals
Rita Corp
Spectrum Quality Products Inc
Stepan Co

Others
Choice Korea Co
Pachem Distributions Inc

Kaolin

UK
Fisher Scientific UK Ltd
JT Baker UK
Paroxite (London) Ltd
Raught Ltd
Sigma-Aldrich Company Ltd
Tennants (Distribution) Ltd
Thew, Arnott and Co Ltd

USA
Sigma-Aldrich Corp
Charles B Chrystal Co Inc
Fisher Scientific
JT Baker Inc
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Voigt Global Distribution LLC
Whittaker Clark, and Daniels Inc
William Ransom & Son plc

Lactic Acid

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Corcoran Chemicals Ltd
Fisher Scientific UK Ltd
JT Baker UK
Peter Whiting (Chemicals) Ltd
Pfanstiehl (Europe) Ltd
Purac Biochem (UK)
Raught Ltd
Tennants (Distribution) Ltd

Other European
Arion & Delahaye
Brenntag AG
Dr Paul Lohmann GmbH KG

USA
AerChem Inc
Amresco Inc
Brenntag Inc
EM Sergeant Pulp & Chemical Co Inc
Fisher Scientific
Inolex Chemical Co
JT Baker Inc
Kraft Chemical Co
Mutchler Inc
Penta Manufacturing Co
Ferro Pfanstiehl Laboratories Inc
Purac America Inc
Rita Corp
Spectrum Quality Products Inc
Triple Crown America
Voigt Global Distribution LLC
Vopak USA Inc

Others
LS Raw Materials Ltd

Lactitol

UK
Danisco Sweeteners Ltd
Purac Biochem (UK)

USA
Danisco USA Inc
Penta Manufacturing Co
Purac America Inc

Lactose, Anhydrous

UK
Borculo Domo Ingredients Ltd
DMV UK

Other European
Borculo Domo Ingredients
DMV Pharma
Molkerei Meggle Wasserburg GmbH

USA
Foremost Farms USA
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Voigt Global Distribution LLC

Others
Lactose New Zealand

Lactose, Monohydrate

UK
Borculo Domo Ingredients Ltd
DMV UK
Forum Biosciences Ltd
Honeywill & Stein
JT Baker UK

Other European
Borculo Domo Ingredients
Brenntag AG
DMV Pharma
Molkerei Meggle Wasserburg GmbH

USA
Brenntag Inc
EMD Chemicals Inc
Foremost Farms USA
JT Baker Inc
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Voigt Global Distribution LLC

Others
Lactose New Zealand
LS Raw Materials Ltd

Lactose, Spray-Dried

UK
Borculo Domo Ingredients Ltd
DMV UK
Forum Biosciences Ltd

Other European
Borculo Domo Ingredients
DMV Pharma
Molkerei Meggle Wasserburg GmbH

USA
Foremost Farms USA
Mutchler Inc
Spectrum Quality Products Inc

Others
Lactose New Zealand

Lanolin

UK
Blagden Specialty Chemicals Ltd
Croda Chemicals Ltd
Fisher Scientific UK Ltd
JT Baker UK
Paroxite (London) Ltd
Raught Ltd

Other European
Brenntag AG

USA
Brenntag Inc
Croda Inc
Fisher Scientific
JT Baker Inc
Kraft Chemical Co
Mutchler Inc
Penta Manufacturing Co
Protameen Chemicals
Rita Corp
Spectrum Quality Products Inc
Voigt Global Distribution LLC

Lanolin, Hydrous

UK
Adina Chemicals Ltd

USA
Lipo Chemicals Inc
Penta Manufacturing Co
Rita Corp
Spectrum Quality Products Inc

Lanolin Alcohols

UK
Croda Chemicals Ltd
Paroxite (London) Ltd

USA
Charkit Chemical Corp
Croda Inc
Kraft Chemical Co
Penta Manufacturing Co
Rita Corp

Lauric Acid

USA
Astro Chemicals Inc

Lecithin

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Aarhus United UK Ltd
Alembic Products Ltd
Allchem Pharma
Forum Biosciences Ltd

Other European
Aarhus United Denmark A/S
Brenntag AG
Lucas Meyer
Stern Lecithin and Soja GmbH

USA
Aarhus United USA Inc
Aceto Corp
Alfa Chem
American Lecithin Co
Ashland
Avatar Corp
Brenntag Inc
Charkit Chemical Corp
Kraft Chemical Co
Lucas Meyer Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America
Voigt Global Distribution LLC
Welch, Holme & Clark Co Inc

Leucine

UK
Sigma-Aldrich Company Ltd

USA
Alfa Chem
Penta Manufacturing Co
Scandinavian Formulas Inc
Seltzer Chemicals Inc

Linoleic Acid

USA
Loos & Dilworth Inc

Macrogol 15 Hydroxystearate

UK
BASF Plc

USA
BASF Corp

Magnesium Aluminum Silicate

UK
Paroxite (London) Ltd

USA
American Colloid Co
Fuji Chemical Industries Health Science (USA) Inc
Kraft Chemical Co
Mutchler Inc
Penta Manufacturing Co
RT Vanderbilt Company Inc
Spectrum Quality Products Inc
Whittaker Clark, and Daniels Inc

Others
Fuji Chemical Industry Co Ltd

Magnesium Carbonate

UK
Chance & Hunt
Courtin & Warner Ltd
Fisher Scientific UK Ltd
Intermag Co Ltd
JT Baker UK
Paroxite (London) Ltd
Tennants (Distribution) Ltd
William Ransom & Son plc

Other European
Brenntag AG
Dr Paul Lohmann GmbH KG
Lehmann & Voss & Co
Magnesia GmbH

USA
AerChem Inc
Alfa Chem
Barrington Chemical Corp
Brenntag Inc
Charkit Chemical Corp
EM Sergeant Pulp & Chemical Co Inc

Fisher Scientific
Gallard-Schlesinger Industries
Generichem Corp
JT Baker Inc
Kraft Chemical Co
Mutchler Inc
Particle Dynamics Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America
Vopak USA Inc
Whittaker Clark, and Daniels Inc

Magnesium Oxide

UK
Fisher Scientific UK Ltd
Intermag Co Ltd
JT Baker UK
Paroxite (London) Ltd
Tennants (Distribution) Ltd

Other European
Brenntag AG
Dr Paul Lohmann GmbH KG
Magnesia GmbH

USA
AerChem Inc
Alfa Chem
Ashland
Barrington Chemical Corp
Brenntag Inc
Fisher Scientific
Gallard-Schlesinger Industries
Generichem Corp
JT Baker Inc
Mutchler Inc
Particle Dynamics Inc
Penta Manufacturing Co
RIA International
Spectrum Quality Products Inc
Vopak USA Inc
Whittaker Clark, and Daniels Inc

Others
LS Raw Materials Ltd

Magnesium Silicate

UK
Intermag Co Ltd

Magnesium Stearate

UK
Allchem Pharma
Corcoran Chemicals Ltd
Fisher Scientific UK Ltd
Intermag Co Ltd
James M Brown Ltd
JRS Pharma Ltd
Paroxite (London) Ltd
Raught Ltd

Other European
Biesterfeld Spezialchemie GmbH
Brenntag AG
Dr Paul Lohmann GmbH KG
J Rettenmaier & Söhne GmbH and Co
Lehmann & Voss & Co
Magnesia GmbH

USA
Aceto Corp
AerChem Inc
Alfa Chem
Ashland
Avatar Corp
Barrington Chemical Corp
Brenntag Inc
Charkit Chemical Corp
EM Industries Inc
EM Sergeant Pulp & Chemical Co Inc
Fisher Scientific
Generichem Corp
JRS Pharma LP
Kraft Chemical Co
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America
Vopak USA Inc
Whittaker Clark, and Daniels Inc

Others
LS Raw Materials Ltd

Magnesium Trisilicate

UK
Courtin & Warner Ltd
Intermag Co Ltd
Raught Ltd
William Ransom & Son plc

Other European
Dr Paul Lohmann GmbH KG
Magnesia GmbH

USA
Gallard-Schlesinger Industries
Generichem Corp
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc

Others
LS Raw Materials Ltd

Malic Acid

UK
Corcoran Chemicals Ltd
DSM UK Ltd
Lonza UK Ltd
Peter Whiting (Chemicals) Ltd
Tennants (Distribution) Ltd
Ubichem plc

Other European
Brenntag AG
DSM Fine Chemicals
Lonza Ltd

USA
AerChem Inc
Ashland
Brenntag Inc
DSM Fine Chemicals Inc
Kraft Chemical Co
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America
Voigt Global Distribution LLC
Vopak USA Inc

Maltitol

UK
Cerestar UK Ltd
Roquette (UK) Ltd

Other European
Cerestar International
Roquette Frères

USA
Ashland
Cargill Corp
Penta Manufacturing Co
Roquette America Inc

Maltitol Solution

UK
Cerestar UK Ltd
Lonza UK Ltd
Roquette (UK) Ltd

Other European
Cerestar International
Lonza Ltd
Roquette Frères

USA
Roquette America Inc

Maltodextrin

UK
Avebe UK Ltd
Cerestar UK Ltd
Corcoran Chemicals Ltd
Roquette (UK) Ltd

Other European
Amylum Ibérica, SA
Avebe Group
Brenntag AG
Cerestar International
Roquette Frères

USA
Ashland
Avebe America Inc
Brenntag Inc
Cargill Corp
Generichem Corp
Grain Processing Corp
Roquette America Inc
Tate & Lyle
Voigt Global Distribution LLC

Maltol

Other European
Helm AG

USA
Ashland
Helm New York Inc
Penta Manufacturing Co

Maltose

UK
Cerestar UK Ltd
Forum Biosciences Ltd
Pfanstiehl (Europe) Ltd

Other European
Cerestar International

USA
Cargill Corp
Penta Manufacturing Co
Ferro Pfanstiehl Laboratories Inc
SPI Pharma Group

Others
Hayashibara Co Ltd

Mannitol

UK
Cerestar UK Ltd
Corcoran Chemicals Ltd
Fisher Scientific UK Ltd
Forum Biosciences Ltd
JT Baker UK
Pfanstiehl (Europe) Ltd
Roquette (UK) Ltd
Ubichem plc

Other European
Brenntag AG
Cerestar International
Helm AG
Roquette Frères

USA
Aceto Corp
AerChem Inc
Alfa Chem
Amresco Inc
Ashland
Brenntag Inc
Cargill Corp
EM Industries Inc
Fisher Scientific
George Uhe Co Inc
JT Baker Inc
Mutchler Inc
Penta Manufacturing Co
Ferro Pfanstiehl Laboratories Inc
RIA International
Roquette America Inc
Spectrum Quality Products Inc
SPI Pharma Group
Voigt Global Distribution LLC
Vopak USA Inc

Others
LS Raw Materials Ltd

Medium-chain Triglycerides

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Alfa Chemicals Ltd/Gattefossé UK
Allchem Pharma
Blagden Specialty Chemicals Ltd
Cognis UK Ltd
Croda Chemicals Ltd
Karlshamns Ltd
Lonza UK Ltd

Other European
Cognis Deutschland GmbH
Gattefossé s.a.
Karlshamns AB
Lonza Ltd

USA
ABITEC Corp
Arista Industries Inc
Cognis Corp
Croda Inc
Gattefossé Corp

Meglumine

UK
EM Industries Inc
Spectrum Quality Products Inc

Menthol

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Courtin & Warner Ltd
Haarmann & Reimer Ltd
Raught Ltd
Stan Chem International Ltd
Thew, Arnott and Co Ltd

Other European
Haarmann & Reimer GmbH
Helm AG

USA
Charkit Chemical Corp
Chart Corp Inc
George Uhe Co Inc
Helm New York Inc
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Voigt Global Distribution LLC

Others
LS Raw Materials Ltd

Methylcellulose

UK
Colorcon Ltd
RW Unwin & Co Ltd

Other European
Brenntag AG

USA
Alfa Chem
Aqualon
Biddle Sawyer Corp
Brenntag Inc
Colorcon
Dow Chemical Co
Mutchler Inc
Spectrum Quality Products Inc

Others
Shin-Etsu Chemical Co Ltd

Methylparaben

UK
Clariant UK Ltd
Cornelius Group plc

Other European
Brenntag AG
Chemag Aktiengesellschaft
Induchem AG

USA
Ashland
Avatar Corp
Brenntag Inc
Charkit Chemical Corp
Kraft Chemical Co
Lipo Chemicals Inc
Napp Technologies Inc
Nipa Laboratories Inc
Penta Manufacturing Co
Protameen Chemicals
Rita Corp
Spectrum Quality Products Inc
Voigt Global Distribution LLC
Vopak USA Inc

Others
LS Raw Materials Ltd
San Fu Chemical Company Ltd

Mineral Oil

UK
British Wax Refining Co
Fisher Scientific UK Ltd
Fuchs Lubricants (UK) plc
JT Baker UK

Other European
Brenntag AG
Parafluid Mineraloelges MBH
Chevron Texaco Global Lubricants Benelux
USOCO BV

USA
Astro Chemicals Inc
Avatar Corp
Brenntag Inc
Fisher Scientific
JT Baker Inc
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America
Vopak USA Inc

Mineral Oil, Light

UK
British Wax Refining Co
Fisher Scientific UK Ltd
Fuchs Lubricants (UK) plc

Other European
Chevron Texaco Global Lubricants Benelux
Parafluid Mineraloelges MBH
USOCO BV

USA
Amresco Inc
Fisher Scientific
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Voigt Global Distribution LLC

Mineral Oil and Lanolin Alcohols

UK
Paroxite (London) Ltd

USA
Protameen Chemicals
Rita Corp

Monoethanolamine

UK
Tennants (Distribution) Ltd

Other European
Brenntag AG

USA
Brenntag Inc
Dow Chemical Co
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America

Monosodium Glutamate

UK
A and E Connock (Perfumery and Cosmetics) Ltd

Other European
Amylum Ibérica, SA
Brenntag AG
Helm AG

USA
Ashland
Brenntag Inc
Delta Distributors Inc
Helm New York Inc
Mutchler Inc
Penta Manufacturing Co
Triple Crown America
Vopak USA Inc
Xinchem Co

Myristic Acid

UK
Brenntag (UK) Ltd

Other European
Cognis Deutschland GmbH

USA
Ashland
Crompton Corp
Penta Manufacturing Co
Ruger Chemical Co Inc

Others
EPS Impex Co.

Neohesperidin Dihydrochalcone

Other European
Exquim S.A.
Natura Internacional S.L.

Nitrogen

UK
Air Liquide UK Ltd
Air Products (Gases) plc
BOC Gases

USA
BOC Gases

Nitrous Oxide

UK
Air Liquide UK Ltd
BOC Gases

USA
BOC Gases

Octyldodecanol

Other European
Cognis Deutschland GmbH

USA
Jarchem Industries Inc

Others
Charles Tennant & Co (Canada) Ltd

Oleic Acid

UK
Croda Chemicals Ltd
Fisher Scientific UK Ltd
H Foster & Co (Stearines) Ltd
JT Baker UK
Kimpton Brothers Ltd
Tennants (Distribution) Ltd
White Sea and Baltic Company Ltd

Other European
Brenntag AG

USA
AerChem Inc
Brenntag Inc
Croda Inc
Delta Distributors Inc
Fisher Scientific
JT Baker Inc
Kraft Chemical Co
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America
Voigt Global Distribution LLC
Vopak USA Inc
Welch, Holme & Clark Co Inc

Others
LS Raw Materials Ltd

Oleyl Alcohol

UK
ISP Europe

Other European
Cognis Deutschland GmbH

USA
Alfa Chem
Croda Inc
Penta Manufacturing Co

Olive Oil

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Aarhus United UK Ltd
Alembic Products Ltd
Paroxite (London) Ltd
Peter Whiting (Chemicals) Ltd
White Sea and Baltic Company Ltd

Other European
Aarhus United Denmark A/S

USA
Aarhus United USA Inc
Arista Industries Inc
Avatar Corp
Charkit Chemical Corp
Hawkins Chemical Inc
Mutchler Inc
Penta Manufacturing Co
Pokonobe Industries Inc
Spectrum Quality Products Inc
Triple Crown America
Voigt Global Distribution LLC

Palmitic Acid

UK
Sigma-Aldrich Company Ltd

Other European
Cognis Deutschland GmbH

USA
Alfa Chem
Ashland
Crompton Corp
Mutchler Inc
Penta Manufacturing Co
Ruger Chemical Co Inc

Others
Charles Tennant & Co (Canada) Ltd

Paraffin

UK
AF Suter and Co Ltd
British Wax Refining Co
Cornelius Group plc
Poth Hille
William Ransom & Son plc

Other European
Brenntag AG
Chevron Texaco Global Lubricants Benelux

USA
Brenntag Inc
Delta Distributors Inc
Koster Keunen Inc
Mutchler Inc
Penta Manufacturing Co
Rita Corp
Spectrum Quality Products Inc
Strahl & Pitsch Inc
USOCO BV
Voigt Global Distribution LLC
Vopak USA Inc

Others
LS Raw Materials Ltd

Peanut Oil

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Aarhus United UK Ltd
Alembic Products Ltd
Alfa Chemicals Ltd
Allchem Pharma
Croda Chemicals Ltd
Efkay Chemicals Ltd
Karlshamns Ltd
White Sea and Baltic Company Ltd

Other European
Aarhus United Denmark A/S
Gattefossé s.a.
Karlshamns AB

USA
Aarhus United USA Inc
Arista Industries Inc
Charkit Chemical Corp
Croda Inc
Gattefossé Corp
Penta Manufacturing Co
Pokonobe Industries Inc
Spectrum Quality Products Inc
Voigt Global Distribution LLC
Welch, Holme & Clark Co Inc

Pectin

UK
ISP Europe
Ingredients Consultancy Ltd, The

USA
Alfa Chem
CP Kelco US Inc
KIC Chemicals Inc
Penta Manufacturing Co
Ruger Chemical Co Inc
TIC Gums

Petrolatum

UK
Efkay Chemicals Ltd
Fuchs Lubricants (UK) plc
Poth Hille

Other European
Brenntag AG
Parafluid Mineraloelges MBH
Chevron Texaco Global Lubricants Benelux
USOCO BV

USA
Avatar Corp
Brenntag Inc
Delta Distributors Inc
Mutchler Inc
Penta Manufacturing Co
Rita Corp
Spectrum Quality Products Inc
Voigt Global Distribution LLC
Vopak USA Inc

Petrolatum and Lanolin Alcohols

UK
Rita Corp

Phenol

UK
Chance & Hunt
Fisher Scientific UK Ltd
JT Baker UK
Tennants (Distribution) Ltd

Other European
Brenntag AG
Chemco France

USA
Amresco Inc
Brenntag Inc
Dow Chemical Co
Fisher Scientific
JT Baker Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Voigt Global Distribution LLC
Vopak USA Inc

Phenoxyethanol

UK
Clariant UK Ltd
Haarmann & Reimer Ltd
Paroxite (London) Ltd
Ubichem plc

Other European
Haarmann & Reimer GmbH
Induchem AG

USA
Kraft Chemical Co
Lipo Chemicals Inc
Nipa Laboratories Inc
Penta Manufacturing Co
Spectrum Quality Products Inc

Phenylethyl Alcohol

UK
Haarmann & Reimer Ltd

Other European
Haarmann & Reimer GmbH

USA
Penta Manufacturing Co
Spectrum Quality Products Inc

Phenylmercuric Acetate

UK
Dow Agrosciences

USA
Dow Agrosciences LLC
George Uhe Co Inc
Spectrum Quality Products Inc

Phenylmercuric Borate

UK
Fluorochem Ltd

USA
Spectrum Quality Products Inc

Phenylmercuric Nitrate

USA
George Uhe Co Inc
Spectrum Quality Products Inc

Phosphoric Acid

UK
JT Baker UK
Peter Whiting (Chemicals) Ltd

Other European
Brenntag AG

USA
Ashland
Brenntag Inc
Delta Distributors Inc
EM Industries Inc
EM Sergeant Pulp & Chemical Co Inc
JT Baker Inc
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Voigt Global Distribution LLC
Vopak USA Inc

Others
LS Raw Materials Ltd

Polacrilin Potassium

UK
Rohm and Haas UK Ltd

USA
Rohm and Haas Co

Poloxamer

UK
BASF Plc

Other European
BASF Aktiengesellschaft

USA
BASF Corp
Penta Manufacturing Co
Spectrum Quality Products Inc

Polycarbophil

USA
Noveon Inc

Polydextrose

UK
Danisco Sweeteners Ltd

USA
Ashland
Danisco USA Inc
Tate & Lyle

Polyethylene Glycol

UK
Adina Chemicals Ltd

Alfa Chemicals Ltd
BASF Plc
Blagden Speciality Chemicals Ltd
Corcoran Chemicals Ltd
Cornelius Group plc
Fisher Scientific UK Ltd
Honeywill & Stein
Sasol UK Ltd
Tennants (Distribution) Ltd

Other European
BASF Aktiengesellschaft
Brenntag AG
Gattefossé s.a.

USA
Ashland
BASF Corp
Brenntag Inc
Dow Chemical Co
Fisher Scientific
Gattefossé Corp
Hawkins Chemical Inc
Lipo Chemicals Inc
Mutchler Inc
Penta Manufacturing Co
Polysciences Inc
Protameen Chemicals
Sasol North America Inc
Spectrum Quality Products Inc
Vopak USA Inc

Others
Aastrid International
LS Raw Materials Ltd

Polyethylene Oxide

UK
Dow Chemical Co

Polymethacrylates

UK
BASF Plc
Eastman Company UK Ltd
Honeywill & Stein
Ubichem plc

Other European
BASF Aktiengesellschaft
Röhm GmbH

USA
BASF Corp
Eastman Chemical Co
Rohm America Inc
Vopak USA Inc

Poly(methyl vinyl ether/maleic anhydride)

UK
Sigma-Aldrich Company Ltd

Other European
Matrix Marketing GmbH

USA
Fisher Scientific

Polyoxyethylene Alkyl Ethers

UK
Adina Chemicals Ltd
BASF Plc
Cognis UK Ltd
Croda Chemicals Ltd
Goldschmidt UK Ltd

Other European
BASF Aktiengesellschaft
Cognis Deutschland GmbH

USA
BASF Corp
Cognis Corp
Croda Inc
ICI Surfactants
Lipo Chemicals Inc
Protameen Chemicals
Rita Corp

Polyoxyethylene Castor Oil Derivatives

UK
Adina Chemicals Ltd
BASF Plc
Cognis UK Ltd
Farma International Inc
Paroxite (London) Ltd
Uniqema
White Sea and Baltic Company Ltd

Other European
BASF Aktiengesellschaft
Cognis Deutschland GmbH

USA
ABITEC Corp
BASF Corp
Cognis Corp
Jeen International Corp
Lipo Chemicals Inc
Protameen Chemicals

Others
Nikko Chemicals Co Ltd

Polyoxyethylene Sorbitan Fatty Acid Esters

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Adina Chemicals Ltd
BASF Plc
Cognis UK Ltd
Croda Chemicals Ltd
Goldschmidt UK Ltd
JT Baker UK
Lonza UK Ltd

Other European
BASF Aktiengesellschaft
Brenntag AG
Cognis Deutschland GmbH
Lonza Ltd

USA
BASF Corp
Brenntag Inc
Cognis Corp
Croda Inc
Hawkins Chemical Inc
JT Baker Inc
Lipo Chemicals Inc
Protameen Chemicals
Rita Corp

Polyoxyethylene Stearates

UK
Adina Chemicals Ltd
BASF Plc

Other European
BASF Aktiengesellschaft

USA
BASF Corp
Lipo Chemicals Inc
Rita Corp

Polyvinyl Acetate Phthalate

UK
Colorcon Ltd

USA
Colorcon

Polyvinyl Alcohol

UK
Acetex Chemicals Ltd
BASF Plc
Blagden Speciality Chemicals Ltd
Nippon Gohsei (UK) Ltd
Honeywill & Stein

Other European
Acetex Chimie SA
BASF Aktiengesellschaft
DuPont de Nemours Int'l SA

USA
Astro Chemicals Inc
BASF Corp
DuPont
Penta Manufacturing Co
Polysciences Inc
Spectrum Quality Products Inc
Vopak USA Inc

Potassium Alginate

UK
ISP Europe

USA
International Specialty Products

Potassium Benzoate

UK
Dow Chemical Company (UK)
DSM UK Ltd

Other European
Brenntag AG
DSM Fine Chemicals
Haltermann GmbH

USA
AerChem Inc
Ashland

Brenntag Inc
Delta Distributors Inc
DSM Fine Chemicals Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America
Voigt Global Distribution LLC
Vopak USA Inc

Potassium Chloride

UK
Fisher Scientific UK Ltd
ISP Europe
JT Baker UK
Peter Whiting (Chemicals) Ltd
Reheis Inc
Stan Chem International Ltd
Tennants (Distribution) Ltd

Other European
Brenntag AG
Dr Paul Lohmann GmbH KG

USA
AerChem Inc
Amresco Inc
Brenntag Inc
Delta Distributors Inc
EM Industries Inc
Fisher Scientific
International Specialty Products
JT Baker Inc
Mutchler Inc
Particle Dynamics Inc
Penta Manufacturing Co
Reheis Inc
Spectrum Quality Products Inc
Vopak USA Inc

Others
LS Raw Materials Ltd

Potassium Citrate

UK
Courtin & Warner Ltd
Fisher Scientific UK Ltd
Peter Whiting (Chemicals) Ltd
Ubichem plc

Other European
Brenntag AG
Dr Paul Lohmann GmbH KG
Jungbunzlauer

USA
AerChem Inc
Ashland
Brenntag Inc
Delta Distributors Inc
Fisher Scientific
Gallard-Schlesinger Industries
Kraft Chemical Co
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Tate & Lyle
Vopak USA Inc

Others
San Fu Chemical Company Ltd

Potassium Hydroxide

UK
Corcoran Chemicals Ltd
Fisher Scientific UK Ltd
JT Baker UK
Peter Whiting (Chemicals) Ltd
Tennants (Distribution) Ltd
Ubichem plc

Other European
Brenntag AG

USA
AerChem Inc
Brenntag Inc
Charkit Chemical Corp
Delta Distributors Inc
EM Industries Inc
Fisher Scientific
JT Baker Inc
Mutchler Inc
Penta Manufacturing Co
Voigt Global Distribution LLC
Vopak USA Inc

Potassium Metabisulfite

UK
Allchem Pharma
Fisher Scientific UK Ltd
Ubichem plc

Other European
Brenntag AG

USA
Brenntag Inc
Fisher Scientific
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Vopak USA Inc

Potassium Sorbate

UK
Blagden Speciality Chemicals Ltd
JT Baker UK
Peter Whiting (Chemicals) Ltd
Tennants (Distribution) Ltd
Thew, Arnott and Co Ltd
White Sea and Baltic Company Ltd

Other European
Brenntag AG
Helm AG

USA
AerChem Inc
Ashland
Avatar Corp
Brenntag Inc
Charkit Chemical Corp
Delta Distributors Inc
Helm New York Inc
JT Baker Inc
Mutchler Inc
Penta Manufacturing Co
Pfizer Corp
Protameen Chemicals
Spectrum Quality Products Inc
Vopak USA Inc

Others
LS Raw Materials Ltd

Povidone

UK
BASF Plc
Blagden Speciality Chemicals Ltd
ISP Europe
Raught Ltd

Other European
August Hedinger GmbH & Co
BASF Aktiengesellschaft
Helm AG

USA
BASF Corp
Hawkins Chemical Inc
Helm New York Inc
International Specialty Products
Napp Technologies Inc
Penta Manufacturing Co

Others
Glide Chem Pvt Ltd

Propionic Acid

UK
Tennants (Distribution) Ltd
White Sea and Baltic Company Ltd

Other European
Brenntag AG

USA
Brenntag Inc
Delta Distributors Inc
Dow Chemical Co
Penta Manufacturing Co
Spectrum Quality Products Inc
Vopak USA Inc

Propyl Gallate

UK
Eastman Company UK Ltd

USA
Aceto Corp
Alfa Chem
Delta Distributors Inc
Eastman Chemical Co
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America

Propylene Carbonate

Other European
Brenntag AG

USA
Brenntag Inc
Penta Manufacturing Co
Vopak USA Inc

Propylene Glycol

UK
Alfa Chemicals Ltd

BASF Plc
Corcoran Chemicals Ltd
Delta Distributors Inc
Eastman Company UK Ltd
Fisher Scientific UK Ltd
JT Baker UK
Lyondell Chemical Europe
Raught Ltd
Sasol UK Ltd
Tennants (Distribution) Ltd

Other European
August Hedinger GmbH & Co
BASF Aktiengesellschaft
Brenntag AG
Gattefossé s.a.

USA
Amresco Inc
Ashland
Avatar Corp
BASF Corp
Brenntag Inc
Dow Chemical Co
Eastman Chemical Co
Fisher Scientific
Gattefossé Corp
JT Baker Inc
Kraft Chemical Co
Lyondell Chemical Co
Mutchler Inc
Penta Manufacturing Co
Rita Corp
Sasol North America Inc
Spectrum Quality Products Inc
Stepan Co
Voigt Global Distribution LLC
Vopak USA Inc

Others
Gadot Petrochemical Industries Ltd

Propylene Glycol Alginate

USA
Delta Distributors Inc
Spectrum Quality Products Inc

Propylparaben

UK
Bayer plc
Clariant UK Ltd

Other European
Chemag Aktiengesellschaft
Induchem AG

USA
Ashland
Avatar Corp
Bayer Corp
Charkit Chemical Corp
Delta Distributors Inc
Kraft Chemical Co
Lipo Chemicals Inc
Napp Technologies Inc
Nipa Laboratories Inc
Penta Manufacturing Co
Protameen Chemicals
Rita Corp
Spectrum Quality Products Inc
Voigt Global Distribution LLC
Vopak USA Inc

Others
LS Raw Materials Ltd
San Fu Chemical Company Ltd

2-Pyrrolidone

UK
BASF Plc
ISP Europe

Other European
BASF Aktiengesellschaft

USA
BASF Corp
EMD Chemicals Inc
International Specialty Products
Kraft Chemical Co

Saccharin

UK
Corcoran Chemicals Ltd
Tennants (Distribution) Ltd

Other European
Brenntag AG
Helm AG
Hermes Sweetners Ltd

USA
Aceto Corp
AerChem Inc
Ashland
Brenntag Inc
Delta Distributors Inc
Helm New York Inc
Mutchler Inc
Penta Manufacturing Co
Pfaltz & Bauer
PMC Specialities Group Inc
Spectrum Quality Products Inc
Triple Crown America
Voigt Global Distribution LLC
Vopak USA Inc

Others
LS Raw Materials Ltd

Saccharin Sodium

UK
Fisher Scientific UK Ltd
JT Baker UK

Other European
Helm AG

USA
Delta Distributors Inc
Fisher Scientific
George Uhe Co Inc
Helm New York Inc
JT Baker Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Voigt Global Distribution LLC

Sesame Oil

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Aarhus United UK Ltd
Adina Chemicals Ltd
Alembic Products Ltd
Croda Chemicals Ltd
Efkay Chemicals Ltd

Other European
Aarhus United Denmark A/S

USA
Aarhus United USA Inc
Arista Industries Inc
Charkit Chemical Corp
Croda Inc
Hawkins Chemical Inc
Lipo Chemicals Inc
Penta Manufacturing Co
Pokonobe Industries Inc
Protameen Chemicals
Spectrum Quality Products Inc
Voigt Global Distribution LLC
Welch, Holme & Clark Co Inc

Shellac

UK
AF Suter and Co Ltd
Cornelius Group plc
Kimpton Brothers Ltd
Mantrose (UK) Ltd
Paroxite (London) Ltd
Thew, Arnott and Co Ltd

Other European
Alland & Robert

USA
Mantrose-Haeuser Co Inc
Penta Manufacturing Co

Simethicone

UK
Dow Corning

USA
Dow Corning

Sodium Alginate

UK
Blagden Speciality Chemicals Ltd

Other European
FMC Biopolymer
Sobel NV

USA
AerChem Inc
FMC Biopolymer
Penta Manufacturing Co
Spectrum Quality Products Inc
Voigt Global Distribution LLC

Sodium Ascorbate

UK
BASF Plc

Peter Whiting (Chemicals) Ltd
Roche Products Ltd

Other European
BASF Aktiengesellschaft
Brenntag AG
Helm AG

USA
AerChem Inc
BASF Corp
Brenntag Inc
Delta Distributors Inc
Helm New York Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Takeda Pharmaceuticals America Inc
Triple Crown America
Vopak USA Inc

Others
LS Raw Materials Ltd
Shijiazhuang Pharmaceutical Group Co Ltd
Takeda Chemical Industries Ltd

Sodium Benzoate

UK
Corcoran Chemicals Ltd
Courtin & Warner Ltd
Dow Chemical Company (UK)
DSM UK Ltd
Fisher Scientific UK Ltd
JT Baker UK
Peter Whiting (Chemicals) Ltd
Tennants (Distribution) Ltd
Ubichem plc

Other European
Brenntag AG
Dr Paul Lohmann GmbH KG
DSM Fine Chemicals
Haltermann GmbH
Helm AG

USA
Aceto Corp
AerChem Inc
Ashland
Brenntag Inc
Delta Distributors Inc
DSM Fine Chemicals Inc
EM Industries Inc
Fisher Scientific
Helm New York Inc
JT Baker Inc
Kraft Chemical Co
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America
Vopak USA Inc

Others
LS Raw Materials Ltd
San Fu Chemical Company Ltd

Sodium Bicarbonate

UK
Blagden Speciality Chemicals Ltd
Brunner Mond (UK) Ltd
Courtin & Warner Ltd
Fisher Scientific UK Ltd
Forum Biosciences Ltd
JT Baker UK
Peter Whiting (Chemicals) Ltd
Raught Ltd
Tennants (Distribution) Ltd

Other European
Brenntag AG

USA
Brenntag Inc
Charkit Chemical Corp
Church and Dwight Co Inc
Delta Distributors Inc
EM Industries Inc
EM Sergeant Pulp & Chemical Co Inc
Fisher Scientific
JT Baker Inc
Mutchler Inc
Penta Manufacturing Co
SPI Pharma Group
Spectrum Quality Products Inc
Triple Crown America
Vopak USA Inc

Sodium Borate

UK
Borax Europe Ltd
JT Baker UK
Sigma-Aldrich Company Ltd

USA
Alfa Chem
Brenntag Inc
EMD Chemicals Inc
Ferro Pfanstiehl Laboratories Inc
Mutchler Inc
Penta Manufacturing Co
Ruger Chemical Co Inc

Others
Highland International
Wuxi Dazhong Chemical Industry Co Ltd

Sodium Chloride

UK
JT Baker UK
Tennants (Distribution) Ltd
Ubichem plc

USA
AerChem Inc
Cargill Corp
Charkit Chemical Corp
Delta Distributors Inc
EM Industries Inc
Fisher Scientific
Hawkins Chemical Inc
JT Baker Inc
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America
Vopak USA Inc

Sodium Citrate Dihydrate

UK
Cerestar UK Ltd
Courtin & Warner Ltd
Fisher Scientific UK Ltd
JT Baker UK
Peter Whiting (Chemicals) Ltd
Roche Products Ltd

Other European
Cerestar International
Dr Paul Lohmann GmbH KG
Jungbunzlauer

USA
AerChem Inc
Cargill Corp
Delta Distributors Inc
EM Industries Inc
Fisher Scientific
JT Baker Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Tate & Lyle
Vopak USA Inc

Others
San Fu Chemical Company Ltd

Sodium Cyclamate

UK
Blagden Speciality Chemicals Ltd

Others
LS Raw Materials Ltd

Sodium Hyaluronate

Other European
Chemos GmbH
Contipro C a.s.
Matrix Marketing GmbH
NovaMatrix

USA
AnMar International

Others
Kibun Food Chemifa Co Ltd
Shangyuchem

Sodium Hydroxide

UK
Fisher Scientific UK Ltd
JT Baker UK
Tennants (Distribution) Ltd
Ubichem plc

Other European
Brenntag AG

USA
AerChem Inc
Brenntag Inc
Charkit Chemical Corp
Delta Distributors Inc
EM Industries Inc
Fisher Scientific
JT Baker Inc
Mutchler Inc

Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America
Vopak USA Inc

Others
LS Raw Materials Ltd

Sodium Lactate

UK
Roquette (UK) Ltd

Other European
Dr Paul Lohmann GmbH KG
Interchim Austria GES.M.B.H
Roquette Frères

USA
Alfa Chem
Amresco Inc
Ashland
EMD Chemicals Inc
Ferro Pfanstiehl Laboratories Inc
Penta Manufacturing Co
Purac America Inc
Ruger Chemical Co Inc

Others
Jiangxi Mosashino Co Ltd

Sodium Lauryl Sulfate

UK
Cognis UK Ltd
Fisher Scientific UK Ltd
Sigma-Aldrich Company Ltd

Other European
Brenntag AG
Cognis Deutschland GmbH

USA
Brenntag Inc
Cognis Corp
Delta Distributors Inc
Fisher Scientific
Kraft Chemical Co
Mutchler Inc
Penta Manufacturing Co
Sigma-Aldrich Corp
Spectrum Quality Products Inc
Stepan Co
Vopak USA Inc

Others
LS Raw Materials Ltd

Sodium Metabisulfite

UK
Corcoran Chemicals Ltd
Fisher Scientific UK Ltd
Peter Whiting (Chemicals) Ltd
Tennants (Distribution) Ltd
Ubichem plc
William Blythe Ltd

Other European
Brenntag AG

USA
AerChem Inc
Brenntag Inc
Delta Distributors Inc
Fisher Scientific
Hawkins Chemical Inc
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America

Others
LS Raw Materials Ltd

Sodium Phosphate, Dibasic

UK
Fisher Scientific UK Ltd
JT Baker UK
Peter Whiting (Chemicals) Ltd
Tennants (Distribution) Ltd
Ubichem plc

Other European
Brenntag AG

USA
AerChem Inc
Brenntag Inc
Delta Distributors Inc
EM Industries Inc
EM Sergeant Pulp & Chemical Co Inc
Fisher Scientific
Gallard-Schlesinger Industries
JT Baker Inc
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America

Sodium Phosphate, Monobasic

UK
Fisher Scientific UK Ltd
JT Baker UK
Peter Whiting (Chemicals) Ltd
Tennants (Distribution) Ltd
Ubichem plc

Other European
Brenntag AG

USA
AerChem Inc
Brenntag Inc
Delta Distributors Inc
EM Industries Inc
EM Sergeant Pulp & Chemical Co Inc
Fisher Scientific
JT Baker Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America

Sodium Propionate

UK
Ubichem plc

Other European
Brenntag AG
Dr Paul Lohmann GmbH KG

USA
Brenntag Inc
Delta Distributors Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America
Vopak USA Inc

Sodium Starch Glycolate

UK
Allchem Pharma
Avebe UK Ltd
Forum Biosciences Ltd
JRS Pharma Ltd

Other European
Avebe Group
J Rettenmaier & Söhne GmbH and Co

USA
Alfa Chem
Avebe America Inc
Barrington Chemical Corp
Generichem Corp
JRS Pharma LP
Mutchler Inc
Penta Manufacturing Co
RIA International
Spectrum Quality Products Inc

Sodium Stearyl Fumarate

UK
Blagden Speciality Chemicals Ltd
Forum Biosciences Ltd
JRS Pharma Ltd

Other European
J Rettenmaier & Söhne GmbH and Co

USA
Aceto Corp
JRS Pharma LP
Spectrum Quality Products Inc

Sodium Sulfite

UK
BASF Plc
JT Baker UK
Sigma-Aldrich Company Ltd

Other European
Chemos GmbH
Degussa AG

USA
Amresco Inc
Ashland
Biddle Sawyer Corp
EMD Chemicals Inc
Penta Manufacturing Co
Ruger Chemical Co Inc
Vopak USA Inc

Others
Xiamen Topusing Chemical Co Ltd

Sorbic Acid

UK
Blagden Speciality Chemicals Ltd
Peter Whiting (Chemicals) Ltd
Tennants (Distribution) Ltd

Other European
Brenntag AG

USA
AerChem Inc
Ashland
Brenntag Inc
Charkit Chemical Corp
Delta Distributors Inc
Penta Manufacturing Co
Protameen Chemicals
Spectrum Quality Products Inc
Triple Crown America
Voigt Global Distribution LLC
Vopak USA Inc

Others
LS Raw Materials Ltd

Sorbitan Esters (Sorbitan Fatty Acid Esters)

A and E Connock (Perfumery and Cosmetics) Ltd
Adina Chemicals Ltd
Cognis UK Ltd
Croda Chemicals Ltd
Goldschmidt UK Ltd
Lonza UK Ltd

Other European
Brenntag AG
Cognis Deutschland GmbH
Lonza Ltd

USA
Ashland
Brenntag Inc
Cognis Corp
Croda Inc
Delta Distributors Inc
Lipo Chemicals Inc
Penta Manufacturing Co
Protameen Chemicals
Spectrum Quality Products Inc
Vopak USA Inc

Sorbitol

UK
Adina Chemicals Ltd
Cerestar UK Ltd
Corcoran Chemicals Ltd
Cornelius Group plc
Forum Biosciences Ltd
Lonza UK Ltd
Pfanstiehl (Europe) Ltd
Roquette (UK) Ltd

Other European
Amylum Ibérica, SA
Biesterfeld Spezialchemie GmbH
Brenntag AG
Cerestar International
Lonza Ltd
Roquette Frères

USA
Alfa Chem
Ashland
Avatar Corp
Barrington Chemical Corp
Brenntag Inc
Cargill Corp
Delta Distributors Inc
EM Industries Inc
EM Sergeant Pulp & Chemical Co Inc
Kraft Chemical Co
Lipo Chemicals Inc
Mutchler Inc
Penta Manufacturing Co
Ferro Pfanstiehl Laboratories Inc
Roquette America Inc
Spectrum Quality Products Inc
SPI Pharma Group
Thornley Company
Triple Crown America
Voigt Global Distribution LLC
Vopak USA Inc

Soybean Oil

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Aarhus United UK Ltd
Corcoran Chemicals Ltd
Croda Chemicals Ltd
Karlshamns Ltd

Other European
Aarhus United Denmark A/S
Karlshamns AB

USA
Aarhus United USA Inc
Arista Industries Inc
Avatar Corp
Charkit Chemical Corp
Croda Inc
Mutchler Inc
Penta Manufacturing Co
Pokonobe Industries Inc
Spectrum Quality Products Inc

Starch

UK
Avebe UK Ltd
Cerestar UK Ltd
National Starch & Chemical Ltd
Paroxite (London) Ltd
Roquette (UK) Ltd
Tennants (Distribution) Ltd

Other European
Amylum Ibérica, SA
Avebe Group
Brenntag AG
Cerestar International
Roquette Frères

USA
Ashland
Avebe America Inc
Brenntag Inc
Cargill Corp
Delta Distributors Inc
Generichem Corp
Grain Processing Corp
Mutchler Inc
National Starch & Chemical Co
Penta Manufacturing Co
Roquette America Inc
Spectrum Quality Products Inc
Voigt Global Distribution LLC

Starch, Pregelatinized

UK
Avebe UK Ltd
Cerestar UK Ltd
Colorcon Ltd
National Starch & Chemical Ltd
Paroxite (London) Ltd
Roquette (UK) Ltd

Other European
Amylum Ibérica, SA
Avebe Group
Cerestar International
Roquette Frères

USA
Avebe America Inc
Cargill Corp
Colorcon
Generichem Corp
Grain Processing Corp
Mutchler Inc
National Starch & Chemical Co
Particle Dynamics Inc
Penta Manufacturing Co
Roquette America Inc

Starch, Sterilizable Maize

UK
Corcoran Chemicals Ltd
Roquette (UK) Ltd

Other European
Amylum Ibérica, SA
Roquette Frères

USA
Roquette America Inc

Stearic Acid

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Cognis UK Ltd
Corcoran Chemicals Ltd
Croda Chemicals Ltd
H Foster & Co (Stearines) Ltd
James M Brown Ltd
JT Baker UK
Kimpton Brothers Ltd
Paroxite (London) Ltd
Poth Hille
Tennants (Distribution) Ltd
Thew, Arnott and Co Ltd
Uniqema
White Sea and Baltic Company Ltd

Other European
Brenntag AG
Cognis Deutschland GmbH

USA
Aceto Corp
Alfa Chem
Ashland
Astro Chemicals Inc
Akzo Nobel Inc
Brenntag Inc
Cognis Corp
Delta Distributors Inc
EM Sergeant Pulp & Chemical Co Inc
Generichem Corp
JT Baker Inc
Koster Keunen Inc
Kraft Chemical Co
Mutchler Inc
Penta Manufacturing Co
Protameen Chemicals
Rita Corp
Spectrum Quality Products Inc
Triple Crown America
Vopak USA Inc

Others
LS Raw Materials Ltd

Stearyl Alcohol

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Aarhus United UK Ltd
Adina Chemicals Ltd
Cognis UK Ltd
Croda Chemicals Ltd
Efkay Chemicals Ltd
Goldschmidt UK Ltd
Kimpton Brothers Ltd

Other European
Aarhus United Denmark A/S
Brenntag AG
Cognis Deutschland GmbH

USA
Aarhus United USA Inc
Avatar Corp
Brenntag Inc
Cognis Corp
Croda Inc
Delta Distributors Inc
Koster Keunen Inc
Kraft Chemical Co
Lipo Chemicals Inc
M Michel and Company Inc
Penta Manufacturing Co
Protameen Chemicals
Rita Corp
Spectrum Quality Products Inc
Stepan Co
Vopak USA Inc

Sucralose

UK
Tate & Lyle plc

USA
McNeil Nutritionals

Sucrose

UK
Fisher Scientific UK Ltd
JT Baker UK
Pfanstiehl (Europe) Ltd
Tate & Lyle plc

Other European
Brenntag AG
NP Pharm

USA
Ashland
Brenntag Inc
Delta Distributors Inc
EM Industries Inc
Fisher Scientific
JT Baker Inc
Mutchler Inc
Penta Manufacturing Co
Ferro Pfanstiehl Laboratories Inc
Spectrum Quality Products Inc
Tate & Lyle
Voigt Global Distribution LLC

Sugar, Compressible

UK
Forum Biosciences Ltd
Wilfrid Smith Ltd

USA
Mutchler Inc
Tate & Lyle

Sugar, Confectioner's

USA
Mutchler Inc

Sugar Spheres

UK
DMV UK
Forum Biosciences Ltd
Honeywill & Stein
JRS Pharma Ltd

Other European
DMV Pharma
J Rettenmaier & Söhne GmbH and Co
NP Pharm

USA
JRS Pharma LP

Sulfobutylether β-Cyclodextrin

USA
Cydex Inc

Sulfuric Acid

UK
Fisher Scientific UK Ltd
JT Baker UK
Tennants (Distribution) Ltd

Other European
Brenntag AG

USA
Ashland
Brenntag Inc
Delta Distributors Inc
Fisher Scientific
JT Baker Inc
Spectrum Quality Products Inc
Triple Crown America
Vopak USA Inc

Suppository Bases, Hard Fat

UK
Aarhus United UK Ltd
Alfa Chemicals Ltd
Blagden Speciality Chemicals Ltd
Cognis UK Ltd
Karlshamns Ltd

Other European
Aarhus United Denmark A/S
Cognis Deutschland GmbH
Gattefossé s.a.
Karlshamns AB

USA
Aarhus United USA Inc
Cognis Corp
Gattefossé Corp
Voigt Global Distribution LLC

Talc

UK
Colin Stewart Minchem Ltd
Fisher Scientific UK Ltd
JT Baker UK
Paroxite (London) Ltd
Pumex (UK) Limited
Tennants (Distribution) Ltd
Thew, Arnott and Co Ltd

Other European
Brenntag AG
Luzenac Europe

USA
Brenntag Inc
Charles B Chrystal Co Inc
EM Sergeant Pulp & Chemical Co Inc
Fisher Scientific
JT Baker Inc
Luzenac America
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America
Voigt Global Distribution LLC
Vopak USA Inc
Whittaker Clark, and Daniels Inc

Tartaric Acid

UK
Fisher Scientific UK Ltd
JT Baker UK
Peter Whiting (Chemicals) Ltd
Tennants (Distribution) Ltd
Ubichem plc

Other European
Arion & Delahaye
Brenntag AG
Dr Paul Lohmann GmbH KG
Helm AG
Pahí SL

USA
Aceto Corp
Ashland
Brenntag Inc
Charkit Chemical Corp
Delta Distributors Inc
EM Sergeant Pulp & Chemical Co Inc
Fisher Scientific
George Uhe Co Inc
Helm New York Inc
JT Baker Inc
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America
Vopak USA Inc

Others
LS Raw Materials Ltd

Thaumatin

Other European
ABCR GmbH

USA
RFI Ingredients

Thimerosal

UK
Sigma-Aldrich Company Ltd
Ubichem plc

USA
Alfa Chem
Charkit Chemical Corp
George Uhe Co Inc
Napp Technologies Inc
Sigma-Aldrich Corp
Spectrum Quality Products Inc

Others
LS Raw Materials Ltd

Thymol

UK
Sigma-Aldrich Company Ltd

Other European
Alfa Aesar Johnson Matthey GmbH

USA
Alfa Chem
EMD Chemicals Inc
Mutchler Inc
Penta Manufacturing Co
Ruger Chemical Co Inc
Thomas Scientific
Vopak USA Inc

Others
Sarman Industries

Titanium Dioxide

UK
A and E Connock (Perfumery and Cosmetics) Ltd
BASF Plc
Cornelius Group plc
Tioxide Europe Ltd
Kronos Ltd
Paroxite (London) Ltd
Peter Whiting (Chemicals) Ltd
Tennants (Distribution) Ltd

Other European
BASF Aktiengesellschaft
Brenntag AG
Chemco France
DuPont de Nemours Int'l SA

USA
AerChem Inc
Ashland
BASF Corp
Brenntag Inc
Delta Distributors Inc
DuPont
Tioxide Americas Inc
Kraft Chemical Co
Mutchler Inc
Penta Manufacturing Co
Spectrum Quality Products Inc
Triple Crown America
Voigt Global Distribution LLC
Vopak USA Inc
Whittaker Clark, and Daniels Inc

Tragacanth

UK
A and E Connock (Perfumery and Cosmetics) Ltd
AF Suter and Co Ltd
Fisher Scientific UK Ltd
Thew, Arnott and Co Ltd

Other European
Alland & Robert

USA
Ashland
Charkit Chemical Corp
Chart Corp Inc
Delta Distributors Inc
Fisher Scientific
Penta Manufacturing Co
Spectrum Quality Products Inc

Triacetin

UK
Eastman Company UK Ltd
Honeywill & Stein
Tennants (Distribution) Ltd

USA
ABITEC Corp
Eastman Chemical Co
Penta Manufacturing Co
Spectrum Quality Products Inc

Tributyl Citrate

UK
Ubichem plc

Other European
Jungbunzlauer

USA
Morflex Inc
Penta Manufacturing Co
Reilly Industries Inc

Triethanolamine

UK
Corcoran Chemicals Ltd
Fisher Scientific UK Ltd
Sasol UK Ltd
Sigma-Aldrich Company Ltd
Tennants (Distribution) Ltd
Ubichem plc

Other European
Brenntag AG

USA
Brenntag Inc
Fisher Scientific
Mutchler Inc
Penta Manufacturing Co
Rita Corp
Sasol North America Inc
Sigma-Aldrich Corp
Spectrum Quality Products Inc
Triple Crown America
Vopak USA Inc

Triethyl Citrate

UK
Alfa Chemicals Ltd/Gattefossé UK
Cognis UK Ltd
Ubichem plc

Other European
Cognis Deutschland GmbH
Gattefossé s.a.
Jungbunzlauer

USA
Charkit Chemical Corp
Cognis Corp
Gattefossé Corp
Jungbunzlauer Inc
Morflex Inc
Penta Manufacturing Co
Reilly Industries Inc

Vanillin

UK
Blagden Speciality Chemicals Ltd
Cornelius Group plc
Fisher Scientific UK Ltd
Raught Ltd
Rhodia Organic Fine Ltd
Tennants (Distribution) Ltd
Ubichem plc

Other European
Biesterfeld Spezialchemie GmbH
Brenntag AG
Helm AG

USA
Ashland
Brenntag Inc
Charkit Chemical Corp
Chart Corp Inc
Delta Distributors Inc
Fisher Scientific
Helm New York Inc
Mutchler Inc
Penta Manufacturing Co
Rhodia Pharma Solutions Inc
Spectrum Quality Products Inc
Triple Crown America
Virginia Dare
Voigt Global Distribution LLC
Vopak USA Inc

Others
LS Raw Materials Ltd

Vegetable Oil, Hydrogenated

UK
Adina Chemicals Ltd
Forum Biosciences Ltd
JRS Pharma Ltd
Karlshamns Ltd
White Sea and Baltic Company Ltd

Other European
Aarhus United Denmark A/S
J Rettenmaier & Söhne GmbH and Co
Karlshamns AB
Chevron Texaco Global Lubricants Benelux

USA
Aarhus United USA Inc
ABITEC Corp
JRS Pharma LP
Lipo Chemicals Inc
Mutchler Inc
Stepan Co

Water

UK
Fisher Scientific UK Ltd
Tennants (Distribution) Ltd

USA
Fisher Scientific
Spectrum Quality Products Inc

Wax, Anionic Emulsifying

UK
Adina Chemicals Ltd
British Wax Refining Co
Cognis UK Ltd
Croda Chemicals Ltd

Other European
Cognis Deutschland GmbH

USA
Cognis Corp
Croda Inc
Lipo Chemicals Inc
Spectrum Quality Products Inc

Wax, Carnauba

UK
AF Suter and Co Ltd
British Wax Refining Co
Cornelius Group plc
Kimpton Brothers Ltd
Paroxite (London) Ltd
Poth Hille
Tennants (Distribution) Ltd
Thew, Arnott and Co Ltd
Ubichem plc

USA
Charkit Chemical Corp
Koster Keunen Inc
Mutchler Inc
Penta Manufacturing Co
Strahl & Pitsch Inc
Whittaker Clark, and Daniels Inc

Wax, Cetyl Esters

UK
A and E Connock (Perfumery and Cosmetics) Ltd
Cognis UK Ltd
Croda Chemicals Ltd

Other European
Cognis Deutschland GmbH

USA
Cognis Corp
Croda Inc
Koster Keunen Inc
Rita Corp
Spectrum Quality Products Inc

Others
LS Raw Materials Ltd

Wax, Microcrystalline

UK
A and E Connock (Perfumery and Cosmetics) Ltd
AF Suter and Co Ltd
British Wax Refining Co
Cornelius Group plc
Kimpton Brothers Ltd
Paroxite (London) Ltd
Poth Hille
Thew, Arnott and Co Ltd

Other European
Chevron Texaco Global Lubricants Benelux
USOCO BV

USA
Avatar Corp
Koster Keunen Inc
Strahl & Pitsch Inc
Voigt Global Distribution LLC
Whittaker Clark, and Daniels Inc

Wax, Nonionic Emulsifying

UK
Adina Chemicals Ltd
Cognis UK Ltd
Croda Chemicals Ltd
Efkay Chemicals Ltd
Paroxite (London) Ltd

Other European
Cognis Deutschland GmbH

USA
Cognis Corp
Croda Inc
Koster Keunen Inc
Lipo Chemicals Inc
Rita Corp

Wax, White

UK
British Wax Refining Co
Cornelius Group plc
Fisher Scientific UK Ltd
Kimpton Brothers Ltd
Paroxite (London) Ltd
Poth Hille
Thew, Arnott and Co Ltd

Other European
Chevron Texaco Global Lubricants Benelux
USOCO BV

USA
Avatar Corp
Charkit Chemical Corp
Fisher Scientific
Koster Keunen Inc
Mutchler Inc
Penta Manufacturing Co
Rita Corp
Spectrum Quality Products Inc
Strahl & Pitsch Inc
Triple Crown America
Voigt Global Distribution LLC
Whittaker Clark, and Daniels Inc

Wax, Yellow

UK
British Wax Refining Co
Cornelius Group plc
Fisher Scientific UK Ltd
Kimpton Brothers Ltd
Paroxite (London) Ltd
Poth Hille
Thew, Arnott and Co Ltd

Other European
Gattefossé s.a.
USOCO BV

USA
Charkit Chemical Corp
Fisher Scientific
Koster Keunen Inc
Mutchler Inc
Penta Manufacturing Co
Rita Corp
Spectrum Quality Products Inc
Strahl & Pitsch Inc
Triple Crown America
Voigt Global Distribution LLC
Whittaker Clark, and Daniels Inc

Xanthan Gum

UK
A and E Connock (Perfumery and Cosmetics) Ltd
AF Suter and Co Ltd
Corcoran Chemicals Ltd
CP Kelco UK Ltd
Rhodia Organic Fine Ltd
Thew, Arnott and Co Ltd

Other European
Biesterfeld Spezialchemie GmbH
Brenntag AG
Jungbunzlauer

USA
Ashland
Brenntag Inc
Charkit Chemical Corp
Chart Corp Inc
CP Kelco US Inc
Delta Distributors Inc
Hawkins Chemical Inc
Penta Manufacturing Co
Rhodia Pharma Solutions Inc
RT Vanderbilt Company Inc
Spectrum Quality Products Inc
TIC Gums
Voigt Global Distribution LLC
Vopak USA Inc

Others
LS Raw Materials Ltd

Xylitol

UK
Cerestar UK Ltd
Danisco Sweeteners Ltd
Forum Biosciences Ltd
Pfanstiehl (Europe) Ltd
Roquette (UK) Ltd
Thew, Arnott and Co Ltd

Other European
Arion & Delahaye
Cerestar International
Helm AG
Roquette Frères

USA
Aceto Corp
Alfa Chem
Cargill Corp
Danisco USA Inc
Delta Distributors Inc
George Uhe Co Inc
Helm New York Inc
Penta Manufacturing Co
Ferro Pfanstiehl Laboratories Inc
Roquette America Inc
Spectrum Quality Products Inc
Triple Crown America
Voigt Global Distribution LLC

Zein

UK
Paroxite (London) Ltd
Ubichem plc

Zinc Acetate

UK
JT Baker UK

Other European
Chemos GmbH
Honeywell Specialty Chemicals Seelze

USA
Alfa Chem
Amresco Inc
EMD Chemicals Inc
Gallard-Schlesinger Industries Inc
Penta Manufacturing Co
Ruger Chemical Co Inc
Thomas Scientific
Universal Preserv-A-Chem Inc
Vopak USA Inc

Zinc Stearate

UK
Allchem Pharma
Fisher Scientific UK Ltd
James M Brown Ltd
JT Baker UK
Paroxite (London) Ltd
Tennants (Distribution) Ltd

Other European
Brenntag AG
Dr Paul Lohmann GmbH KG

USA
Aceto Corp
Alfa Chem
Brenntag Inc
Fisher Scientific
George Uhe Co Inc
Kraft Chemical Co
Mutchler Inc
Penta Manufacturing Co
RIA International
Spectrum Quality Products Inc
Triple Crown America
Voigt Global Distribution LLC
Vopak USA Inc
Whittaker Clark, and Daniels Inc

Suppliers List: UK

3M United Kingdom Plc
3M Centre
Cain Road
Bracknell
RG12 8HT
Tel: +44 (0)8705 360036
Web: www.3m.com
Trade names: *CoTran.*

A and E Connock (Perfumery and Cosmetics) Ltd
Alderholt Mill House
Fordingbridge
SP6 1PU
Tel: +44 (0)142 565 3367
Fax: +44 (0)142 565 6041
E-mail: sales@connock.co.uk
Web: www.connock.co.uk

Aarhus United UK Ltd
King George Dock
Kingston-upon-Hull
HU9 5PX
Tel: +44 (0)1482 701 271
Fax: +44 (0)1482 709 447
E-mail: uk.info@aarhusunited.com
Web: www.aarhusunited.com/uk
Trade names: *Aextreff CT; Albutein; Colzao CT; Cremao CS-34; Cremao CS-36; Hyfatol 16-95; Hyfatol 16-98; Shogun CT.*

Acetex Chemicals Ltd
Canterbury House
41/53 Gosport Street
Lymington
SO41 9BB
Tel: +44 (0)1590 688 222
Fax: +44 (0)1590 688 333
E-mail: sales@acetex.co.uk
Web: www.acetex-eu.com

Adina Chemicals Ltd
12 Chapman Way
Tunbridge Wells
TN2 3EF
Tel: +44 (0)1892 517585
Fax: +44 (0)1892 517565
E-mail: sales@adina.co.uk
Web: www.adina.co.uk
Trade names: *Lipocol; Lipocol C; Lipolan; Liponate IPP; Lipovol SES.*

AF Suter and Co Ltd
Thames House
18 Park Street
London
SE1 9EQ
Tel: +44 (0)207 403 6555
Fax: +44 (0)207 378 8582
E-mail: afsuter@afsuter.com
Web: www.afsuter.com
Trade names: *Swanlac.*

Air Liquide UK Ltd
Cedar House
39 London House
Reigate
RH2 9QE
Tel: +44 (0)737 241133
Fax: +44 (0)737 241842
Web: www.airliquide.com

Air Products (Gases) plc
2 Millennium Gate
Westmere Drive
Crewe
CW1 6AP
Tel: +44 (0)800 389 0202
Fax: +44 (0)1932 258 502

Air Products plc *see* Air Products (Gases) plc

Alembic Products Ltd
Unit 2 Brymau Est.
River Lane
Saltney
Chester
CH4 8RB
Tel: +44 (0)1244 680147
Fax: +44 (0)1244 680155
Web: www.alembicproducts.co.uk

Alfa Chemicals Ltd *see* Alfa Chemicals Ltd/Gattefossé UK
Trade names: *Resomer.*

Alfa Chemicals Ltd/Gattefossé UK
Arc House
Terrace Road South
Binfield
Bracknell
RG42 4PZ
Tel: +44 (0)1344 861800
Fax: +44 (0)1344 451400
E-mail: info@alfa-chemicals.co.uk
Web: www.alfa-chemicals.co.uk
Trade names: *Labrafac CC; Precirol ATO 5; Resomer.*

Allchem Pharma
Broadway House
21 Broadway
Maidenhead
SL6 1NJ
Tel: +44 (0)1753 443322
Fax: +44 (0)1753 443323
E-mail: info@allchem.co.uk
Web: www.allchem.co.uk
Trade names: *Bergabest; Elcema; Genetron; Genetron 142b; Genetron 152a; Sternpur; Vivastar P; Vivapur; Vivasol.*

Alpha Therapeutic Europe Limited *see* Aarhus United UK Ltd

Avebe UK Ltd
Thornton Hall
Thornton Curtis
Ulceby
DN39 6XD
Tel: +44 (0)1469 532 222
Fax: +44 (0)1469 531 488
Web: www.avebe.com
Trade names: *Paselli MD10 PH; Perfectamyl D6PH; Prejel; Primellose; Primogran W; Primojel.*

Baker *see* JT Baker UK

BASF Plc
PO Box 4
Earl Road
Cheadle Hulme
Cheadle
SK8 6QG
Tel: +44 (0)161 485 6222
Fax: +44 (0)161 486 0891
Web: www.basf.de/uk
Trade names: *Cremophor; Cremophor A; Kollicoat MAE 30 D; Kollicoat MAE 30 DP; Kollidon; Kollidon CL; Kollidon CL-M; Kollidon VA 64; Lutrol E; Luviskol VA; Plurafac; Soluphor P; Solutol HS 15.*

Bayer plc
Bayer House
Strawberry Hill
Newbury
RG14 1JA
Tel: +44 (0)1635 563000
Fax: +44 (0)1635 563 393
E-mail:
corporate.communications@bayer.co.uk
Web: www.bayer.co.uk
Trade names: *Solbrol A; Solbrol P.*

Blagden Specialty Chemicals Ltd
Osprey House
Black Eagle Square
Westerham
TN16 1PA
Tel: +44 (0)1959 562000
Fax: +44 (0)1959 565511
E-mail: sales@blagdenspecchem.co.uk
Web: www.blagdenspecchem.co.uk

BOC Gases
The Priestley Centre
10 Priestly Road
Surrey Research Park
Guildford
GU2 5XY
Tel: +44 (0)800 111333
Web: www.boc.com

Borax Europe Ltd
1A The Guildford Business Park
Guildford
GU2 8XG
Tel: +44 (0)1483 242 000
Fax: +44 (0)1483 242 001

Borculo Domo Ingredients Ltd
Riverside House
Brymau Three Estate
River Lane
Saltney
Chester
CH4 8RQ
Tel: +44 (0)1244 680127
Fax: +44 (0)1244 671703
E-mail: sales@bdiuk.co.uk
Web: www.borculodomo.com
Trade names: *Lactochem; Lactopress Anhydrous; Lactopress Spray-Dried.*

BP plc
1 St James's Square
London
SW1Y 4PD
Tel: +44 (0)20 7496 4000
Fax: +44 (0)20 7496 4630
Web: www.bp.com

Brenntag (UK) Ltd
Ham Lane
Kingswinford
DY6 7JU
Tel: +44 (0)1384 400222
Fax: +44 (0)1384 400020
E-mail: sales@brenntag.co.uk
Web: www.brenntag.co.uk

British Traders & Shippers Ltd *see* Nippon Gohsei (UK) Ltd

British Wax Refining Co
62 Holmethorpe Avenue
Holmethorpe Industrial Estate
Surrey
RH1 2NL
Tel: +44 (0)1737 761242
Fax: +44 (0)1737 761472

Brunner Mond (UK) Ltd
PO Box 4
Mond House
Northwich
CW8 4DT
Tel: +44 (0)1606 724000
Fax: +44 (0)1606 781353
Web: www.brunnermond.com

Cerestar UK Ltd
Trafford Park
Manchester
M17 1PA
Tel: +44 (0)161 872 5959
Fax: +44 (0)161 848 9034
Web: www.cerestar.com
Trade names: *Cavitron; C*Ascend; C*Eridex; C*Pharm; C*PharmDex; C*PharmDry; C*PharmGel; C*PharmMaltidex; C*PharmMannidex; C*PharmSorbidex; C*PharmSweet.*

Chance & Hunt
Alexander House
Crown Gate
Runcorn
WA7 2UP
Tel: +44 (0)1928 793000
Fax: +44 (0)1928 714351
E-mail: passport@chance-hunt.com
Web: www.chance-hunt.com

Clariant UK Ltd
Calverleyy Lane
Horsforth
Leeds
LS18 4RP
Tel: +44 (0)113 258 4646
Fax: +44 (0)113 239 8473
Web: www.clariant.co.uk
Trade names: *Ethyl parasept; Nipacide PX; Nipanox BHA; Nipanox BHT; Nipantiox 1-F; Tylopur; Tylopur MH; Tylopur MHB; Tylose CB; Tylose MB; Tylose MH; Tylose MHB; Tylose PHA.*

Cognis UK Ltd
Charleston Road
Hardley
Southampton
SO45 3ZG
Tel: +44 (0)2380 894666
Fax: +44 (0)2380 243113
Web: www.uk.cognis.com

Trade names: *Copherol F1300; Cutina CP; Cutina GMS; Cutina HR; Dehymuls; Emulgade 1000NI; Eumulgin; Hydagen CAT; Lanette O; Majsao CT; Monomuls 90-O18; Myritol; Novata; Texapon K12P.*

Colin Stewart Minchem Ltd
Weaver Valley Road
Winsford
CW7 3BU
Tel: +44 (0)1606 868 200
Fax: +44 (0)1606 868 268
Web: www.csminchem.co.uk
Trade names: *Magsil Star.*

Colloides Naturels UK Ltd
The Triangle Business Centre
Exchange Square
Manchester
M4 3TR
Tel: +44 (0)161 838 5744
Fax: +44 (0)161 838 5746
Web: www.cniworld.com

Colorcon Ltd
Flagship House
Victory Way
Crossways
Dartford
DA2 6QD
Tel: +44 (0)1322 293000
Fax: +44 (0)1322 627200
E-mail: infouk@colorcon.com
Web: www.colorcon.com
Trade names: *Methocel; Opaseal; Phthalavin; Starch 1500 G; Surelease; Sureteric.*

Connock *see* A and E Connock (Perfumery and Cosmetics) Ltd

Corcoran Chemicals Ltd
Oak House
Oak Close
Wilmslow
SK9 6DF
Tel: +44 (0)1625 532 731
Fax: +44 (0)1625 539 096
E-mail: a.bryne@corcoran-chemicals.co.uk
Web: www.corcoranchemicals.com
Trade names: *Maldex; Meritol.*

Cornelius Group plc
Cornelius House
Dunmow Road
Woodside
Bishop's Stortford
CM23 5RG
Tel: +44 (0)1279 714 300
Fax: +44 (0)1279 714 320
E-mail: sales.dept@cornelius.co.uk
Web: www.cornelius.co.uk
Trade names: *Tronox.*

Courtin & Warner Ltd
19 Phoenix Place
Lewes
BN7 1JX
Tel: +44 (0)1273 480611
Fax: +44 (0)1273 472249
Web: www.c-and-w.co.uk

Coventry Chemicals Ltd
Woodhams Road
Siskin Drive
Coventry
CV3 4FX
Tel: +44 (0)24 7663 9739
Fax: +44 (0)24 7663 9717

CP Kelco UK Ltd
Cleeve Court
Cleeve Road
Leatherhead
KT22 7UD
Tel: +44 (0)1372 369 400
Fax: +44 (0)1372 369 401
Web: www.cpkelco.com
Trade names: *Keltrol; Xantural.*

Croda Chemicals Ltd
Cowick Hall
Snaith
Goole
DN14 9AA
Tel: +44 (0)1405 860551
Fax: +44 (0)1405 860205
E-mail: healthcare-sales@croda-oleochemicals.com
Web: www.croda.co.uk
Trade names: *Byco; Cithrol; Crill; Crillet; Crodacid; Crodacol C70; Crodacol C90; Crodacol CS90; Crodacol S95; Crodamol IPM; Crodamol IPP; Crodamol SS; Croderol; Crodex A; Crodex N; Croduret; Crossential 094; Etocas; Hartolan; Polawax; Volpo.*

Danisco Sweeteners Ltd
41–51 Brighton Road
Redhill
RH1 6YS
Tel: +44 (0)1737 773732
Fax: +44 (0)1737 773117
E-mail: sweeteners@danisco.com
Web: www.daniscosweeteners.com
Trade names: *Litesse.*

Degussa Hüls Ltd *see* Degussa Ltd

Degussa Ltd
Winterton House
Winterton Way
Macclesfield
SK11 0LP
Tel: +44 (0)1625 503050
Fax: +44 (0)1625 502096
Web: www.degussa.com
Trade names: *Aerosil.*

DMV UK
PO Box 11
Teddington
TW11 8YG
Tel: +44 (0)20 8943 5220
Fax: +44 (0)20 8943 5231
E-mail: robern@dmv-international.com
Trade names: *Nu-Core; Nu-Pareil PG; Pharmacel; Pharmatose DCL 11; Pharmatose DCL 14; Pharmatose DCL 15; Pharmatose DCL 21; Pharmatose DCL 22; Pharmatose 50M; Pharmatose 80M; Pharmatose 90M; Pharmatose 100M; Pharmatose 110M; Pharmatose 125M; Pharmatose 150M; Pharmatose 200M; Pharmatose 350M; Pharmatose 450M; Primellose.*

Dow Agrosciences
Latchmore Court
Brand Street
Hitchin
SG5 1HZ
Tel: +44 (0)146 245 7272
Fax: +44 (0)146 242 6605
E-mail: fhihotl@dow.com
Web: www.dowagro.com
Trade names: *Gallotox; Liquiphene.*

Dow Chemical Company (UK)
2 Heathrow Boulevard
284 Bath Road
West Drayton
UB7 0DQ
Tel: +44 (0)208 917 5000
Fax: +44 (0)208 917 5400
Web: www.dow.com

Dow Corning
Center Northern Europe
Meriden Business Park
Copse Drive
Allesley
Coventry
CV5 9RG
Tel: +44 (0)1676 528000
Fax: +44 (0)1676 528001
Web: www.dowcorning.com
Trade names: *Dow Corning 245 Fluid; Dow Corning 246 Fluid; Dow Corning 345 Fluid; Dow Corning Q7-2243 LVA; Dow Corning Q7-2587; Dow Corning Q7-9120.*

DSM UK Ltd
DSM House
Papermill Drive
Redditch
B98 8QJ
Tel: +44 (0)1527 590590
Fax: +44 (0)1527 590555
Web: www.dsm.com

Eastman Company UK Ltd
European Technical Centre
Acornfield Road
Knowsley Industrial Park North
Kirkby
L33 7UF

Tel: +44 (0)151 547 2002
Fax: +44 (0)151 548 5100
Trade names: *Eastacryl 30D; Eastman Vitamin E TPGS; Tenox BHA; Tenox BHT; Tenox PG.*

Edward Mendell *see* JRS Pharma Ltd

Efkay Chemicals Ltd
Allen House
The Maltings
Station Road
Sawbridgeworth
CM21 9JX
Tel: +44 (0)1279 721 888
Fax: +44 (0)1279 722 261
E-mail: efkachem@aol.com
Web: www.efkay.com

Fisher Scientific UK Ltd
Bishop Meadow Road
Loughborough
LE11 5RG
Tel: +44 (0)1509 231166
Fax: +44 (0)1509 231893
E-mail: info@fisher.co.uk
Web: www.fisher.co.uk

Fluorochem Ltd
Wesley Street
Old Glossop
SK13 7RY
Tel: +44 (0)1457 868921
Fax: +44 (0)1457 869360/860927
E-mail: enquiries@fluorochem.co.uk
Web: www.fluorochem.net

Forum Biosciences Ltd
41–51 Brighton Road
Redhill
RH1 6YS
Tel: +44 (0)1737 773711
Fax: +44 (0)1737 773116
Web: www.forum.co.uk
Trade names: *Candex; Compactrol; Dextrofin; Effer-Soda; Emcocel; Emcompress; Emdex; Explotab; Lubritab; Mannogem; ProSolv; Pruv; Satialgine H8; Sorbogem; Xylitab.*

Foster & Co *see* H Foster & Co (Stearines) Ltd

Fuchs Lubricants (UK) plc
New Century Street
Hanley
Stoke-on-Trent
ST1 5HU
Tel: +44 (0)8701 200 400
Fax: +44 (0)1782 202072/3
E-mail: contact-uk@fuchs-oil.com
Web: www.fuchslubricants.com
Trade names: *Silkolene; Sirius.*

Global Ceramic Materials Ltd
Milton Works
Leek New Road
Milton
Stoke-on-Trent
ST2 7PX
Tel: +44 (0)1782 537297
Fax: +44 (0)1782 537867
E-mail: info@Globalcm.co.uk

Goldschmidt UK Ltd
Tego House
Chippenham Drive
Kingston
Milton Keynes
MK10 OAF
Tel: +44 (0)1908 582250
Fax: +44 (0)1908 582254
Web: www.goldschmidtsurfactants.com
Trade names: *ABIL; Tegin; Tegin 503; Tegin 515; Tegin 4100; Tegin M; Tegosept E; Tegosoft M.*

Grace Davison
Oak Park Business Centre
Alington Road
Little Barford
St Neots
PE19 6WL
Tel: +44 (0)1480 324430
Fax: +44 (0)1480 324433
Web: www.grace.com

Haarmann & Reimer Ltd
Fieldhouse Lane
Marlow
SL7 1TB
Tel: +44 (0)1628 472 051
Fax: +44 (0)1635 562 007
E-mail: usuk@hr-gmbh.de
Trade names: *Arosol.*

Haltermann Ltd *see* Dow Chemical Company (UK)

Hercules Ltd
Aqualon Division
Langley Road
Salford
M6 6JU
Tel: +44 (0)161 736 4461
Fax: +44 (0)161 745 7009
Trade names: *Aqualon; Aquasorb; Blanose; Culminal MHEC; Klucel; Natrosol.*

H Foster & Co (Stearines) Ltd
103 Kirkstall Road
Leeds
LS3 1JL
Tel: +44 (0)113 243 9016
Fax: +44 (0)113 242 2418
E-mail: info@hfoster.co.uk
Web: www.hfoster.co.uk

Honeywill & Stein
Times House
Throwley Way
Sutton
SM1 4AF
Tel: +44 (0)208 770 7090
Fax: +44 (0)208 770 7295
E-mail: info@honeywill.co.uk
Web: www.honeywill.co.uk
Trade names: *Ac-Di-Sol; Aquacoat cPD; Aquacoat ECD; Avicel PH; Blanose; Celphere; Gelcarin; Klucel; Myvatex; Myvaplex 600 P; Natrosol; NPTAB; Pluriol E; Protacid; Protanal; Wyndale.*

Huntsman Tioxide *see* Tioxide Europe Ltd

Ingredients Consultancy Ltd, The
PO Box 66
Tewkesbury
GL20 6YQ
Tel: +44 (0)1684 59 4949
Fax: +44 (0)1684 59 4748
E-mail: info@theingredients.co.uk
Web: theingredients.co.uk

Intermag Co Ltd
Felling Industrial Estate
Bath Road
Gateshead
NE10 0LG
Tel: +44 (0)191 495 2220
Fax: +44 (0)191 438 4717

ISP Europe
Waterfield
Tadworth
KT20 5HQ
Tel: +44 (0)20 7519 5054
Fax: +44 (0)20 7519 5056
Trade names: *Celex; Germall 115; Kelcosol; Keltone; Pharmasolve; Plasdone; Plasdone S-630; Polyplasdone XL; Polyplasdone XL-10.*

James M Brown Ltd
Napier Street
Fenton
Stoke-on-Trent
ST4 4NX
Tel: +44 (0)1782 744171
Fax: +44 (0)1782 744473
E-mail: sales@jamesmbrown.co.uk
Web: www.jamesmbrown.co.uk

JRS Pharma Ltd
Church House
48 Church Street
Reigate
RH2 0SN
Tel: +44 (0)1737 222323
Fax: +44 (0)1737 222545
E-mail: techsales@jrspharma.co.uk
Web: www.jrspharma.com
Trade names: *Emcompress Anhydrous; Candex; Compactrol; Emcompress; Emcocel; Emdex; Explotab; Lubritab; ProSolv; Pruv; Satialgine H8.*

JT Baker UK
Mallinkrodt Baker UK
107/112 Leadenhall Street
London
EC3A 4AH
Tel: +44 (0)1908 506000
Fax: +44 (0)1908 503290
E-mail:
jtbaker.uk@emea.tycohealthcare.com

Web: www.jtbaker.com
Trade names: *HyQual.*

Karlshamns Ltd
220 Wincolmlee
Hull
HU2 0PX
Tel: +44 (0)1482 586747
Fax: +44 (0)1482 587004
E-mail: info@karlshamns.co.uk
Web: www.karlshamns.com
Trade names: *Akofine; Akosoft; Akosol; Lipex 107; Lipex 108; Lipex 200; Lipex 204.*

Kelco *see* CP Kelco UK Ltd

Kimpton Brothers Ltd
10–14 Hewett Street
London
EC2A 3RL
Tel: +44 (0)20 7456 9999
Fax: +44 (0)20 7247 2784/7375 3584
E-mail: info@kimpton.co.uk
Web: www.kimpton.com

Kronos Ltd
Barons Court
Manchester Road
Wilmslow
SK9 1BQ
Tel: +44 (0)1625 547200
Fax: +44 (0)1625 533123
E-mail: sales@kronosww.com
Trade names: *Kronos 1171.*

Lanxess Ltd
Lichfield Road
Burton-Trent
DE14 3WH
Tel: +44 (0)1283 714200
Fax: +44 (0)1283 714201
E-mail: john.bridges@lanxess.com
Web: www.bayferrox.de
Trade names: *Bayferrox 306; Bayferrox 920Z.*

Leading Solvent Supplies Ltd
Rudgate
Tockwith
York
YO26 7QF
Tel: +44 (0)1423 358000
Fax: +44 (0)1423 358923
E-mail: sales@Leading-Solvent.co.uk
Web: www.Leading-Solvent.co.uk

Lloyd Ltd *see* WS Lloyd Ltd

Lonza UK Ltd
228 Bath Road
Slough
SL1 4DX
Tel: +44 (0)1753 777000
Fax: +44 (0)1753 777001
E-mail: contact.slough@lonza.com
Web: www.lonzagroup.com
Trade names: *Aldo MO; Glycon; Glycon G-100; Hyamine 1622; Hyamine 3500.*

Lyondell Chemical Europe
Bridge Avenue
Maidenhead
SL6 1YP
Tel: +44 (0)1628 775000
Fax: +44 (0)1628 775180
E-mail: david.hancock@lyondell.com
Web: www.lyondell.com

Mantrose (UK) Ltd
Unit 7B Northfield Farm
Great Shefford
RG17 7BY
Tel: +44 (0)1488 648 988
Fax: +44 (0)1488 648 890
Web: www.mbzgroup.com
Trade names: *CertiSeal; Mantrolac R-49.*

Mast Group Ltd
Mast House
Derby Road
Bootle
L20 1EA
Tel: +44 (0)151 9337277
Fax: +44 (0)151 9441332
Web: www.mastgrp.com

Mendell *see* JRS Pharma Ltd

Messer UK Ltd *see* Air Liquide UK Ltd

National Starch & Chemical Ltd
Prestbury Court
Greencourts Business Park
333 Styal Road
Manchester
M22 5LW
Tel: +44 (0)161 435 3200
Fax: +44 (0)161 435 3300
Web: www.nationalstarch.com
www.excipients.com
Trade names: *National 78-1551; Purity 21; Purity 826; Unipure LD; Unipure WG220.*

Nipa Laboratories Ltd *see* Clariant UK Ltd

Nippon Gohsei (UK) Ltd
Soarnol House
Kingston upon Hull
HU12 8DS
Tel: +44 (0)1482 333320
Fax: +44 (0)1482 333325
E-mail: info@nippon-gohsei.com
Web: www.nippon-gohsei.com
Trade names: *Gohsenol.*

Nutrinova UK Ltd
Atrium Court
The Ring
Bracknell
RG12 1BW
E-mail:
caroline.boardman@nutrinova.co.uk
Web: www.nutrinova.com
Trade names: *Sunett.*

Paroxite (London) Ltd
Office Unit 2
7 Dryden Court
Renfrew Road
Kennington
London
SE11 4NH
Tel: +44 (0)20 7735 2425
Fax: +44 (0)20 7735 4408
E-mail: paroxite@clara.co.uk
Trade names: *Albagel; EmCon CO; Fancol; Hygum TP-1; Phenoxen; Pure-Dent; Pure-Dent B851; Spress B820; Waglinol 6014.*

PB Gelatins UK Ltd
Treforest
Pontypridd
CF37 5SQ
Tel: +44 (0)1443 849300
Fax: +44 (0)1443 844209
E-mail: nop@tessenderlo.com
Web: www.tessenderlogroup.com
Trade names: *Cryogel; Instagel; Solugel.*

Penwest Ltd *see* JRS Pharma Ltd

Peter Whiting (Chemicals) Ltd
1 Oil Mill Lane
Hammersmith
London
W6 9UA
Tel: +44 (0)20 8741 4025
Fax: +44 (0)20 8741 1737
E-mail: sales@whiting-chemicals.co.uk
Web: www.whiting-chemicals.co.uk

Pfanstiehl (Europe) Ltd
Unit 27 Meridian House
Road One
Winsford Industrial Estate
Winsford
CW7 3QG
Tel: +44 (0)1606 559163
Fax: +44 (0)1606 559641
E-mail: custserv@pfaneur.u-net.com
Web: www.pfanstiehl.com

PMC Chemicals Ltd
12 Downham Chase
Timperley
Altrincham
WA15 7TJ
Tel: +44 (0)161 904 0499
Fax: +44 (0)161 904 7080
E-mail: sales@pmcchemicals.com
Web: pmcchemicals.com

Poth Hille
37 High Street
Stratford
London
E15 2QD
Tel: +44 (0)20 8534 7091
Fax: +44 (0)20 8534 2291
Web: www.poth-hille.co.uk

Pumex (UK) Limited
Unit D4
Grampian House
Meridian Gate
Marsh Wall
London
E14 9YT
Tel: +44 (0)20 7363 5456
Fax: +44 (0)20 7363 5780
E-mail: info@pumex.co.uk
Web: www.pumex.co.uk
Trade names: *Magsil Osmanthus.*

Purac Biochem (UK)
50–54 St Paul's Square
Birmingham
B3 1QS
Tel: +44 (0)121 236 1828
Fax: +44 (0)121 236 1401
E-mail: puk@purac.com
Web: www.purac.com
Trade names: *Lacty; Purasorb; Purasorb PD; Purasorb PDL; Pursasorb PDLG; Purasorb PG; Pursasorb PL.*

Raught Ltd
38 Cambridge Road
Barking
IG11 8NW
Tel: +44 (0)20 8591 6933
Fax: +44 (0)20 8507 8066
E-mail: info@raught.co.uk
Web: www.raught.co.uk

Reheis
Willowbank House
97 Oxford Road
Highbridge Estate
Uxbridge
UB8 1LU
Tel: +44 (0)1895 819316
Fax: +44 (0)1895 819333
Web: www.reheis.com
Trade names: *Rehydraphos.*

Rhodia Organic Fine Ltd
PO Box 46
St Andrews Road
Avonmouth
Bristol
BS11 9YF
Tel: +44 (0)117 948 4242
Fax: +44 (0)117 948 4249
Trade names: *A-TAB; DI-TAB; Meyprodor; Meyprofin; Meyprofleur; Meyprogat; Rhodiarome; Rhodigel; Rhovanil; TRI-TAB; TRI-CAL WG.*

Roche Products Ltd
40 Broadwater Road
PO Box 8
Welwyn Garden City
AL7 3AY
Tel: +44 (0)170 736 6000
Fax: +44 (0)170 733 8297
Web: www.roche.com

Rohm and Haas UK Ltd
Heckmondwike Road
Dewsbury Moor
Dewsbury
WF13 3NG
Tel: +44 (0)1924 403367
Fax: +44 (0)1824 405166
Web: www.rohmhaas.com/ionexchange
Trade names: *Amberlite IRP-88.*

Roquette (UK) Ltd
Sallow Road
Corby
NN17 5JX
Tel: +44 (0)1536 273000
Fax: +44 (0)1536 263873
E-mail: roquette.uo.phar@wanadoo.fr
Web: www.roquette.com
Trade names: *Flolys; Fluidamid R444P; Glucidex; Keoflo ADP; Kleptose; Lycadex PF; Lycasin 80/55; Lycasin HBC; Lycatab C; Lycatab DSH; Lycatab PGS; Maltisorb; Maltisorb 75/75; Neosorb; Pearlitol; Roclys; Roferose; Xylisorb.*

RW Unwin & Co Ltd
Prospect Place
Welwyn
AL6 9EW
Tel: +44 (0)1438 716441
Fax: +44 (0)1438 716067
E-mail: sales@rwunwin.co.uk
Web: www.rwunwin.co.uk
Trade names: *Aqoat; Aqoat AS-HF/HG; Aqoat AS-LF/LG; Aqoat AS-MF/MG; Metolose.*

Sasol UK Ltd
No. 1 Hockley Court
2401 Stratford Road
Hockley Heath
Solihull
B94 6NW
Tel: +44 (0)1564 783 060
Fax: +44 (0)1564 784 088
E-mail: hugh.odonnell@sasol.com
Web: www.sasol.com
Trade names: *Imwitor 191; Imwitor 900; Lipoxol.*

Shin-Etsu Chemical Co Ltd *see* RW Unwin & Co Ltd

Sigma-Aldrich Company Ltd
Fancy Road
Poole
BH12 4QH
Tel: +44 (0)1747 833000
Fax: +44 (0)1202 712239
E-mail: ukcustsv@europe.sial.com
Web: www.sigma-aldrich.com
Trade names: *Thimerosal Sigmaultra.*

Sparkford Chemicals Ltd
58 The Avenue
Southampton
SO17 2 1XS
Tel: +44 (0)23 8022 8747
Fax: +44 (0)23 8021 0240
E-mail: info@sparkford.co.uk
Web: www.sparkford.co.uk

Stan Chem International Ltd
4 Kings Road
Reading
RG1 3AA
Tel: +44 (0)118 958 0247
Fax: +44 (0)118 958 9580
E-mail: info@stanchem.co.uk
Web: www.stanchem.co.uk

Tate & Lyle plc
Head Office
Sugar Quay
Lower Thames Street
London
EC3R 6DQ
Tel: +44 (0)20 7626 6525
Fax: +44 (0)20 7623 5213
Web: www.tate-lyle.co.uk

Tennants (Distribution) Ltd
Hazelbottom Road
Cheatham
Manchester
M8 0GR
Tel: +44 (0)161 2054454
Fax: +44 (0)161 2035985

Thew, Arnott and Co Ltd
Newman Works
270 London Road
Wallington
SM6 7DJ
Tel: +44 (0)20 8669 3131
Fax: +44 (0)20 8669 7747
E-mail: sales@thewarnott.co.uk
Web: www.thewarnott.co.uk

Tioxide Europe Ltd
(Huntsman Tioxide)
Tees Road
Hartlepool
TS25 2DD
Tel: +44 (0)1642 376376
Fax: +44 (0)1642 376446
Web: www.huntsman.com
Trade names: *Tioxide.*

Ubichem plc
Mayflower Close
Chandlers Ford Industrial Estate
Eastleigh
SO53 4AR
Tel: +44 (0)23 8026 3030
Fax: +44 (0)23 8026 3012
E-mail: sales@ubichem.com
Web: www.ubichem.com

Uniqema
PO Box 90
Wilton Centre
Middlesbrough
TS90 8JE
Tel: +44 (0)16 4245 4144
Fax: +44 (0)16 4243 7374
Web: www.uniqema.com
Trade names: *Estol IPM; Pricerine; Pristerene.*

Unwin *see* RW Unwin & Co Ltd

Wacker Chemicals Ltd
120 Bridge Road
Chertsey
T16 8LA
Tel: +44 (0)870 048202
Fax: +44 (0)870 0480203
Web: www.wacker.com
Trade names: *Cavamax W6 Pharma; Cavamax W7 Pharma; Cavamax W8 Pharma; Wacker HDK.*

White Sea and Baltic Company Ltd
Arndale House
Otley Road
Headingley
Leeds
LS6 2UU
Tel: +44 (0)113 230 4774
Fax: +44 (0)113 230 4770
E-mail: sales@whitesea.co.uk
Web: www.whitesea.co.uk

Whiting (Chemicals) Ltd *see* Peter Whiting (Chemicals) Ltd

Wilfrid Smith Ltd
Elm House
Medlicott Close
Oakley Hay
Corby
NN18 9NF
Tel: +44 (0)1536 460020
Fax: +44 (0)1536 462400
Web: www.wilfrid-smith.co.uk

William Blythe Ltd
Church
Accrington
BB5 4PD
Tel: +44 (0)125 432 0000
Fax: +44 (0)125 432 0001
E-mail: info@wm-blythe.co.uk
Web: www.wm-blythe.co.uk

William Ransom & Son plc
Alexander House
40A Wilbury Way
Hitchin
SG4 0AP
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Fax: +44 (0)1462 420 528
E-mail: info@williamransom.com
Web: www.williamransom.com

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7 Redgrove House
Stonards Hill
Epping
CM16 4QQ
Tel: +44 (0)1992 572670
Fax: +44 (0)1992 578074
E-mail: enquiries@wslloyd.com
Web: www.wslloyd.com

Xyrofin (UK) Ltd *see* Danisco Sweeteners Ltd

Suppliers List: Other European

Aarhus Oliefabrik A/S *see* Aarhus United Denmark A/S

Aarhus United Denmark S/S
MP Brunns Gade 27
PO Box 50
DK-8100 Aarhus C
Denmark
Tel: +45 8730 6000
Fax: +45 8730 6012
E-mail: aarhus@aarhusunited.com
Web: www.aarhusunited.com/dk
Trade names: *Aextreff CT; Albutein; Colzao CT; Cremao CS-34; Cremao CS-36; Hyfatol 16-95; Hyfatol 16-98; Shogun CT.*

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F-92205 Neuilly Sur Seine Cedex
France
Tel: +33 1 47 38 97 00
Fax: +33 1 47 38 97 32
E-mail: info.siege@acetex-eu.com
Web: www.acetex-eu.com

Ajinomoto Switzerland AG
Innere Güterstrasse 2-4
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CH-6304 Zug
Switzerland
Tel: +41 41 728 66 66
Fax: +41 41 728 65 65/66
Web: www.ajinomoto.ch

Akzo Nobel Functional Chemicals bv
Barchman Wuytierslaan 10
PO Box 247
NL-3800 AE Amersfoort
Netherlands
Tel: +31 33 467 6767
Fax: +31 33 467 6146
Trade names: *Akucell; Dissolvine.*

Alfa Aesar Johnson Matthey GmbH
Postbox 11 07 65
D-76057 Karlsruhe
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Tel: +49 721 84007 280
Fax: 49 721 84007 300
E-mail: gcat@matthey.com
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Amylum Ibérica, SA
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Avda. Salvador Allende, 76-78
50015 Zaragoza
Spain
Tel: +34 976 738 100
Fax: +34 976 738 128
E-mail: spain@amylum.com
Web: www.amylumgroup.com
Trade names: *Fructamyl; Glucodry; Glucomalt; Glucosweet; Maldex; Merigel; Meritena; Meritol; Mylose.*

Arion & Delahaye
Grote Markt.7
B-2000
Antwerpen
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9640 AA Veendam
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Fax: +31 598 66 43 68
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Web: www.avebe.com
Trade names: *Paselli MD10 PH; Perfectamyl D6PH; Prejel; Primellose; Primogran W; Primojel.*

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Tel: +49 621 60 42525
Fax: +49 621 60 97060
E-mail: info.service@basf-ag.de
Web: www.basf-ag.de
Trade names: *Cremophor; Cremophor A; Kollicoat MAE 30 D; Kollicoat MAE 30 DP; Kollidon; Kollidon CL; Kollidon CL-M; Kollidon VA 64; Lutrol E; Luviskol VA; Myacide; Plurafac; Soluphor P.*

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Binger Strasse 173
D-55216 Ingelheim
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Tel: +49 6132 77 3978
Fax: +49 6132 77 4227
Web: www.boehringer-ingelheim.com/finechem
Trade names: _Resomer._

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8017 JD Zwolle
PO Box 449
NL-8000 AK Zwolle
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Tel: +31 38 46 77 444
Fax: +31 38 46 77 579
Web: www.borculodomo.com
Trade names: _Lactochem; Lactopress Anhydrous; Lactopress Spray-Dried._

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Fax: +49 208 7828 635
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Fax: +32 56 77 57 11
E-mail: infor@brenntag.be
Web: www.brenntag.be
Trade names: _Tri-Cafos._

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Josef-Bautz-Strasse 15
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Germany
Tel: +49 6181 505150
Fax: +49 6181 505201
Web: www.cabot-corp.com/cabosil
Trade names: _Cab-O-Sil._

Cargill Cerestar BVBA
Office Park Mechelen
Bedrijvenlaan 9
2800 Mechelen
Belgium
Tel: +32 15 400 411
Fax: +32 15 400 410
Trade names: _C*PharmSweet; Isomaltidex 16500._

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F-59482 Haubourdin Cedex BP109
France
Tel: +33 (0)3 20 44 3535
Fax: +33 (0)3 20 44 3567
Web: www.cerestar.com
Trade names: _Cavitron; C*Ascend; C*Eridex; C*Pharm; C*PharmDex; C*PharmDry; C*PharmGel; C*PharmMaltidex; C*PharmMannidex; C*PharmSorbidex; C*PharmSweet._

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Fax: +49 (0) 36 78 38 82 25 2
E-mail: customerservice@cff.de
Web: www.cff.de
Trade names: _Sanacel._

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Clariant GmbH
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Tel: +49 6196 75760
Trade names: _Tylopur; Tylopur MH; Tylopur MHB; Tylose CB; Tylose MB; Tylose MH; Tylose MHB; Tylose PHA._

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Fax: +49 211 798 2431
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Web: www.cognis.com
Trade names: _Copherol F1300; Cutina CP; Cutina GMS; Cutina HR; Emulgade 1000NI; Eumulgin; Eutanol G PH; HD-Eutanol V PH; Hydagen CAT; Lanette 16; Lanette O; Monomuls 90-O18; Myritol; Novata; Texapon K12P._

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Fax: +33 2 32 83 19 19
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Web: www.cniworld.com

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Fax: +49 69 218 3218
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Trade names: _Aerosil._

Degussa Hüls AG _see_ Degussa AG

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Web: www.dmv-international.com
Trade names: _Nu-Core; Nu-Pareil PG; Pharma-Carb; Pharmacel; Pharmatose DCL 11; Pharmatose DCL 14; Pharmatose DCL 15; Pharmatose DCL 21; Pharmatose DCL 22; Pharmatose 50M; Pharmatose 80M; Pharmatose 90M; Pharmatose 100M; Pharmatose 110M; Pharmatose 125M; Pharmatose 150M; Pharmatose 200M; Pharmatose 350M; Pharmatose 450M; Primellose._

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Fax: +31 46 477 3172
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Web: www.dsm.com

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CH-1218 Le Grand Saconnex
Geneva
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Tel: + 41 22 717 5111
Fax: + 41 22 717 5500
Web: www.dupont.com
Trade names: *Dymel; Dymel 134a/P; Dymel 142b; Dymel 152a; Dymel 227 EA/P; Dymel A; Elvanol; TiPure.*

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S. Cugat del Valles
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Spain
Tel: 93 5044400
Fax: 93 5894502
E-mail: exquim@ferrergrupo.com
Web: www.exquim.com
Trade names: *Citrosa.*

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Tel: +32 2 775 8311
Fax: +32 2 775 8300
E-mail: pharm_info@fmc.com
Web: www.fmcbiopolymer.com
Trade names: *Ac-Di-Sol; Aquacoat cPD; Aquacoat ECD; Avicel PH; Celphere; Gelcarin; Marine Colloids; Protacid; Protanal; SeaSpen PF; Viscarin.*

Gattefossé s.a.
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Fax: +33 1 4147 1929
E-mail: infopharma@gattefosse.com
Web: www.gattefosse.fr
Trade names: *Apifil; Compritol 888 ATO; Labrafac CC; Peceol; Precirol ATO 5.*

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Division of Symrise GmbH & Co KG
Muehlenfeldstrasse 1
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Fax: +49 5531 901649
Web: www.symrise.de
Trade names: *Arosol.*

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Hedinger GmbH *see* August Hedinger GmbH & Co

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E-mail: info@hermesetas.com
Web: www.hermesetas.com
Trade names: *Hermesetas.*

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Fax: +31 (0)413 340797
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Trade names: *HMS.*

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Fax: +49 7967 152345
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Web: www.jrs.de
Trade names: *Arbocel; Vivapress Ca; Vivapur; Vivasol; Vivastar P.*

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St Alban-Vorstadt 90
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Tel: +41 61 295 51 00
Fax: +41 61 295 51 08
E-mail: jblint@jungbunzlauer.com
Web: www.jungbunzlauer.com
Trade names: *Citrofol AI.*

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Tel: +46 (0)454 82000
Fax: +46 (0)454 82810
E-mail: info@karlshamns.se
Web: www.karlshamns.com
Trade names: *Akofine; Akosoft; Akosol; Lipex 107; Lipex 200.*

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Fax: +49 4101 3053 90
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Tel: +41 61 316 81 11
Fax: +41 61 316 91 11
E-mail: info@lonzagroup.com
Web: www.lonzagroup.com
Trade names: *Aldo MO; Glycon; Glycon G-100; Hyamine 1622.*

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Trade names: *Luzenac Pharma; Superiore.*

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Fax: +49 4131 8710 50
E-mail: info@magnesia.de
Web: www.magnesia.de
Trade names: *MagGran CC.*

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Meggle Gmbh *see* Molkerei Meggle Wasserburg GmbH

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Germany
Tel: +49 80 71 73 487
Fax: +49 80 71 73 320
E-mail: service.pharma@meggle.de
Web: www.meggle-pharma.de
Trade names: *CapsuLac; FlowLac 100; GranuLac; Inhalac; PrismaLac; SacheLac; SorboLac; SpheroLac; Tablettose.*

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Fax: 34 96 5606076
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D-40210 Düsseldorf
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Fax: +49 211 328 231, 133003
Web: www.nippon-soda.co.jp
Trade names: *Nisso HPC.*

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Web: www.noviantgroup.com
Trade names: *Finnfix; Nymcel; Nymcel ZSC; Nymcel ZSX.*

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Fax: +33 134 877 896
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Web: www.nppharm.fr
Trade names: *Cutina HR; Ethispheres; NPTAB; Suglets.*

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Fax: +49 69305 815412
E-mail: harflett@nutrinova.com
Web: www.nutrinova.com
Trade names: *Sunett.*

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Fax: +32 (0)16 801 308
E-mail: group@orafti.com
Web: www.orafti.com
Trade names: *Raftiline.*

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Web: www.palatinit.de
Trade names: *Beneo; GalenIQ; Palatinit.*

Palatinit Süßungsmittel GmbH *see* Palatinit GmbH

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Web: www.tessenderlo.com
Trade names: *Cryogel; Instagel; Solugel.*

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Trade names: *Rehydraphos.*

Rettenmaier *see* J Rettenmaier & Söhne GmbH and Co

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Web: www.roehm.com
Trade names: *Eudragit.*

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E-mail: roquette.uo.phar@wanadoo.fr
Web: www.roquette.fr
Trade names: *Flolys; Fluidamid R444P; Glucidex; Keoflo ADP; Kleptose; Lycadex PF; Lycasin 80/55; Lycasin HBC; Lycatab C; Lycatab DSH; Lycatab PGS; Maltisorb; Maltisorb 75/75; Neosorb; Pearlitol; Roclys; Roferose; Xylisorb.*

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Fax: +31 165 56 7796
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Web: www.sensus.nl
Trade names: *Frutafit.*

SKW Biosystems *see* Sobel NV

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Fax: +49 7063 512 55
Web: www.solvay-fluor.com
Trade names: *Solkane 142b; Solkane 152a.*

Solvay Fluor und Derivative *see* Solvay Fluor GmbH

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Südzucker AG *see* Palatinit GmbH

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Texas Global Products Benelux *see* Chevron Texaco Global Lubricants Benelux

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Business Line Biotechnology
Johannes Hess Str. 24
D-84489 Burghausen
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Fax: +49 8677 833 100
Web: www.wacker-biochem.com
Trade names: *Cavamax W6 Pharma; Cavamax W7 Pharma; Cavamax W8 Pharma; Wacker HDK.*

Suppliers List: USA

3M Drug Delivery Systems
3M Center
St Paul
MN 55144-1000
Tel: +1 888 364 3577
Web: www.3m.com
Trade names: *CoTran.*

Aarhus United USA Inc
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Port Newark
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Tel: +1 973 344 1300
Fax: +1 973 344 9049
E-mail: us.soles@aarhusunited.com
Web: www.aarhusunited.com
Trade names: *Aextreff CT; Albutein; Colzao CT; Cremao CS-34; Cremao CS-36; Hyfatol 16-95; Hyfatol 16-98; Shogun CT.*

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Tel: +1 614 429 6464
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E-mail: sales@abiteccorp.com
Web: www.abiteccorp.com
Trade names: *Acconon; Capmul GMO; Capmul GMS-50; Captex 300; Captex 355; Captex 500; Sterotex; Sterotex HM.*

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Trade names: *Aeropres 17; Aeropres 31; Aeropres 108.*

AE Staley Mfg Co *see* Tate & Lyle

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Houston
TX 77056
Tel: +1 800 820 2522

Akzo Nobel
525 West Van Burewn Street
Chicago
l 60607
Tel: +1 312 5447000
E-mail: CSRUS@Akzo-Nobel.com
Web: www.akzonobelusa.com
Trade names: *Elfan 240; Dissolvine; Kessco IPM 95; Kortacid 1895.*

Aldrich *see* Sigma-Aldrich Corp

Alfa Chem
2 Harbor Way
King's Point
NY 11024
Tel: +1 516 504 0059
Fax: +1 516 504 0039
E-mail: alfachem1@aol.com
Web: www.alfachem1.com

Alzo International Inc
650 Jernee Mill Road
Sayreville
NJ 08872
Tel: +1 732 254 1901
Fax: +1 732 254 4423
E-mail: carolyn.zofchak@mail.alzointernational.com
Web: www.alzointernational.com
Trade names: *Wickenol 111.*

American Colloid Co
1500 West Shure Drive
Arlington Heights
IL 60004
Tel: +1 847 392 4600
Fax: +1 847 506 6199
Web: www.colloid.com
Trade names: *Magnabrite; Polargel.*

American Lecithin Co
115 Hurley Road
Unit 2B
Oxford
CT 06478
Tel: +1 203 262 7100
Fax: +1 203 262 7101
Web: www.americanlecithin.com
Trade names: *Phosal 53 MCT; Phospholipon 100 H.*

Amresco Inc
30175 Solon Industrial Parkway
Solon
OH 44139
Tel: +1 800 829 2805
Fax: +1 440 349 1182
E-mail: info@amresco-inc.com
Web: www.amresco-inc.com

AnMar International
PO Box 2343
Bridgeport
CT 06608
Tel: +1 203 336 8330
Fax: +1 203 336 5508
E-mail: BlancoAnMar@snet.net
Web: www.anmarinternational.com

Aqualon
(Division of Hercules Inc)
Hercules Plaza
1313 North Market Street
Wilmington
DE 19894-0001
Tel: +1 302 594 5000
Fax: +1 302 594 5400
E-mail: aqualon-us@herc.com
Web: www.herc.com
Trade names: *Aqualon; Benecel; Benecel MHPC; Blanose; Culminal MC; Culminal MHEC; Galactosol; Genu; Klucel; Natrosol.*

Arista Industries Inc
557 Danbury Road
Wilton
CT 06897
Tel: +1 800 255 6457
Fax: +1 203 761 4980
E-mail: info@aristaindustries.com
Web: www.aristaindustries.com

Ashland
PO Box 2219
Columbus
OH 43216 2219
Tel: +1 614 790 3333
Web: www.ashchem.com

Astro Chemicals Inc
64–94 Shaw's Lane
PO Box 2248
Springfield
MA 01102
Tel: +1 413 781 7240
Fax: +1 413 781 7246
Web: www.astrochemicals.com
Trade names: *Airvol; Drakeol; Hystrene; Hystrene 9512; Industrene; Nipasol M.*

Avanti Polar Lipids Inc
700 Industrial Park Drive
Alabaster
AL 35007-9105
Tel: +1 800 227 0651
Fax: +1 205 6630756
E-mail: info@avantilipids.com
Web: www.avantilipids.com

Avatar Corp
500 Central Avenue
University Park
IL 60466
Tel: +1 708 534 5511
Fax: +1 708 534 0123
E-mail: sales@avatarcorp.com
Web: www.avatarcorp.com
Trade names: *Avatech; Avol; Citation; LSC 5050; LSC 6040; Snow white.*

Avebe America Inc
South Rail Road
North Charleston
SC 29420
Tel: +1 843 863 1055
Web: www.avebe.com
Trade names: *Paselli MD10 PH; Perfectamyl D6PH; Prejel; Primellose; Primogran W; Primojel.*

Aventis Behring LLC *see* ZLB Behring

Barrington Chemical Corp *see* Barrington Nutritionals Inc

Barrington Nutritionals Inc
500 Mamaroneck Ave
Harrison
NY 10528
Tel: +1 914 381 3500
Fax: +1 914 381 2232
E-mail: info@barringtonchem.com
Web: www.barringtonchem.com

BASF Corp
100 Campus Drive
Florham Park
NJ 07932
Tel: +1 973 245 6000
Fax: +1 973 245 6002
Web: www.basf.com
Trade names: *Cremophor; Cremophor A; Kollicoat MAE 30 D; Kollicoat MAE 30 DP; Kollidon; Kollidon CL; Kollidon CL-M; Kollidon VA 64; Lutrol E; Luviskol VA; Myacide; Plurafac; Soluphor P.*

Bayer Corp
100 Bayer Road
Building 14
Pittsburgh
PA 15205-9741
Tel: +1 412 777 3934
Fax: +1 412 778 6526
Web: www.bayer.com
Trade names: *Solbrol A; Solbrol P.*

BF Goodrich Speciality Chemicals *see* Noveon Inc

Biddle Sawyer Corp
21 Penn Plaza
360 West 31st Street
New York
NY 10001-2727
Tel: +1 212 736 1580
Fax: +1 212 239 1089
E-mail: BSC@biddlesawyer.com
Web: www.biddlesawyer.com
Trade names: *Metolose.*

BOC Gases
575 Mountain Avenue
Murray Hill
NJ 07974 2082
Tel: +1 908 464 8100
Web: www.boc.com

Boehringer Ingelheim Chemicals Inc
PO Box 1658
3330 South Crater Road
Petersburg
VA 23805
Tel: +1 804 863 0098
Fax: +1 804 862 3246

E-mail: cvance@bichemicals.com
Web: www.boehringer-ingelheim.com/finechem
Trade names: *Resomer.*

BP Inc
535 Madison Avenue
New York
NY 10022-4212
Tel: +1 212 421 5010
Fax: +1 212 421 5084
Web: www.bp.com

Brainerd Chemical Company Inc
1200 North Peoria
PO Box 470010
Tulsa
OK 74147-0010
Tel: +1 918 622 1214
Fax: +1 918 632 0851
E-mail: sales@brainerdchemical.com
Web: www.brainerdchemical.com

Brenntag Inc
PO Box 13786
Reading
PA 19612 3786
Tel: +1 610 926 6100
Fax: +1 610 926 0420
E-mail: brenntag@brenntag.com
Web: www.brenntagnorthamerica.com
Trade names: *Sequestrene AA.*

Burlington Bio-medical and Scientific Corp
71 Carolyn Boulevard
Farmingdale
NY 11735
Tel: +1 631 694 4700
Fax: +1 631 694 9177
Trade names: *Bitterguard.*

Cabot Corp
5401 Venice Ave
Albuquerque
NM 87113
Tel: +1 505 342 1492
Web: www.cabot-corp.com/cabosil
Trade names: *Cab-O-Sil; Cab-O-Sil M-5P.*

Cargill Corp
Cargill Office Center
PO Box 9300
Minneapolis
MN 55440 9300
Tel: +1 952 742 7575
Web: www.cargill.com
Trade names: *Cavitron.*

Cerestar USA Inc *see* Cargill Corp

Charkit Chemical Corp
9 Old Kings Highway South
PO Box 1725
Darien
CT 06820 1725
Tel: +1 203 655 3400
Fax: +1 203 655 8643
E-mail: sales@charkit.com
Web: www.charkit.com

Charles B Chrystal Co Inc
30 Vesey Street
New York
NY 10007
Tel: +1 212 227 2151
Fax: +1 212 233 7916
E-mail: info@cbchrystal.com
Web: www.cbchrystal.com
Trade names: *Lion; Purtalc; Sim 90.*

Charles Bowman & Co
PO Box 2427
Holland
MI 49424-2427
Tel: +1 616 786 4000
Fax: +1 616 786 2864
E-mail: cbc@charlesbowman.com
Web: www.charlesbowman.com

Chart Corp Inc
787 East 27th Street
Paterson
NJ 07504
Tel: +1 201 345 5554
Fax: +1 201 345 2139

Church and Dwight Co Inc
469 North Harrison Street
Princeton
NJ 08543
Tel: +1 800 221 0453
Fax: +1 609 497 7176
Web: www.ahperformance.com

Clariant Corp
4000 Monroe Road
Charlotte
NC 28205
Tel: +1 704 331 7000
Fax: +1 704 331 7810
Web: www.clariant.com
Trade names: *Tylopur; Tylopur MH; Tylopur MHB; Tylose CB; Tylose MB; Tylose MH; Tylose MHB; Tylose PHA.*

Cognis Corp
North America Headquarters
5051 Estecreek Drive
Cincinnati
OH 45232-1446
Tel: +1 513 482 3000
Fax: +1 513 482 5503
Web: www.na.cognis.com
Trade names: *Copherol F1300; Cutina CP; Cutina GMS; Cutina HR; Emulgade 1000NI; Eumulgin; Hydagen CAT; Lanette 16; Lanette O; Monomuls 90-O18; Myritol; Novata; Texapon K12P.*

Colloides Naturels Inc
1170 US Highway 22
Suite 204
Bridgewater
NJ 08807
Tel: +1 908 707 9400
Fax: +1 908 707 9405

Colorcon
415 Moyer Boulevard
West Point
PA 19486
Tel: +1 215 699 7733
Fax: +1 215 661 2605
E-mail: infous@colorcon.com
Web: www.colorcon.com
Trade names: *Methocel; Opaseal; Phthalavin; Starch 1500 G; Surelease; Sureteric.*

CP Kelco US Inc
1000 Parkwood Circle
Suite 1000
Atlanta
GA 30339
Tel: +1 678 247 7300
Fax: +1 302 594 6260
Web: www.cpkelco.com
Trade names: *Keltose; Keltrol; Xantural.*

Croda Inc
300-A Columbus Circle
Edison
NJ 08837
Tel: +1 732 417 0800
Fax: +1 732 417 0804
E-mail: marketing@crodausa.com
Web: www.crodausa.com
Trade names: *Byco; Crill; Crillet; Crodacol C90; Crodacol CS90; Crodacol S95; Crodamol GTC/C; Crodamol IPM; Crodamol IPP; Crodamol SS; Crodex A; Crodex N; Croduret; Crossential 094; Etocas; Hartolan; Polawax; Volpo.*

Crompton Corp
Global Corporate Headquarters
199 Benson Road
Middlebury
CT 06749
Tel: +1 203 573 2000
Trade names: *Sentry.*

CTD Inc
27317 NW 78th Avenue
High Springs
FL 32643
Tel: +1 386 454 0887
Fax: +1 386 454 8134
Web: www.cyclodex.com

Cultor Food Science *see* Danisco USA Inc

Cydex Inc
12980 Metcalf Avenue
Suite 470
Overland Park
KS 66213
Tel: +1 913 685 8850
Fax: +1 913 685 8856
E-mail: cdinfo@cydexinc.com
Web: www.cydex.com
Trade names: *Captisol.*

Danisco Cultor America Inc *see* Danisco USA Inc

Danisco USA Inc
440 Saw Mill River Road
Ardsley
NY 10502-2605
Tel: +1 913 764 8100
Fax: +1 914 674 6542
E-mail: sweeteners@danisco.com
Web: www.daniscosweeteners.com
Trade names: *Litesse.*

Degussa Corp
379 Interpace Parkway
PO Box 677
Parsipanny
NJ 07054-0677
Tel: +1 973 541 8000
Fax: +1 973 541 8501
Web: www.degussa.com
Trade names: *Aerosil.*

Degussa Hüls Corp *see* Degussa Corp

Delta Distributors Inc
610 Fisher Road
Longview
TX 75604
Tel: +1 903 759 7151
Fax: +1 903 759 7548

Dow Agrosciences LLC
9330 Zionsville Road
Indianapolis
IN 46268
Tel: +1 317 337 3000
Fax: +1 800 905 7326
Web: www.dowagro.com

Dow Chemical Co
2030 Dow Center
Midland
MI 48642
Tel: +1 989 636 1000
Fax: +1 989 636 3518
Web: www.dow.com
Trade names: *Carbowax; Carbowax Sentry; Cellosize HEC; Ethocel; Methocel; Optim; Versene Acid.*

Dow Corning
Corporate Center
PO Box 994
Midland
MI 48686-0994
Tel: +1 989 496 4400
Fax: +1 989 496 6731
Web: www.dowcorning.com
Trade names: *Dow Corning 245 Fluid; Dow Corning 246 Fluid; Dow Corning 345 Fluid; Dow Corning Q7-2243 LVA; Dow Corning Q7-2587; Dow Corning Q7-9120.*

DSM Fine Chemicals Inc
Park 80 West
Plaza Two
Saddle Brook
NJ 07663 5817
Tel: +1 (201) 226 7403
Fax: +1 (201) 845 44 06
Web: www.dsmfinechemicals.com

DuPont
Packaging and Industrial Polymers
Barley Mill Plaza 26-2122
Lancaster Pike, Route 141
PO Box 80026
Wilmington
DE 19880-0026
Tel: +1 302 922 5225
Fax: +1 302 922 3495
E-mail: info@dupont.com
Web: www.dupont.com
Trade names: *Dymel 142b; Dymel 152a; Dymel 227 EA/P; Dymel A; Elvanol; TiPure.*

DuPont (Packaging and Industrial Polymers) *see* DuPont

Eastech Chemical Inc
5700 Tacony Street
Philadelphia
PA 19135
Tel: +1 215 537 1000
Fax: +1 215 537 8575
E-mail: mail@eastechchemical.com
Web: www.eastechchemical.com
Trade names: *Unimate GMS; Unimate IPP.*

Eastman Chemical Co
100 North Eastman Road
PO Box 511
Kingsport
TN 37662-5075
Tel: +1 423 229 2000
Fax: +1 423 229 2145
Web: www.eastman.com
Trade names: *Eastacryl 30D; Eastman Vitamin E TPGS; Tenox BHA; Tenox BHT; Tenox PG.*

Edward Mendell Co *see* JRS Pharma LP

EMD Chemicals Inc
480 South Democrat Road
Gibbstown
NJ 08027
Tel: +1 856 423 6300
Fax: +1 856 423 4389
E-mail: emdinfo@emdchemicals.com
Web: www.emdchemicals.com
Trade names: *Sorbitol Instant.*

EM Industries Inc *see* EMD Chemicals Inc

EM Sergeant Pulp & Chemical Co Inc
6 Chelsea Road
Clifton
NJ 07012
Tel: +1 973 4729111
Fax: +1 973 472 5686
E-mail: info@sergeantchem.com
Web: www.sergeantchem.com

Farma International Inc
9501 Old Dixie Highway
Miami
FL 33156
Tel: +1 305 670 4416
Fax: +1 305 670 4417
E-mail: farma2@aol.com
Web: www.farmainternational.com
Trade names: *Eumulgin; Veegum HS.*

Ferro Pfanstiehl Laboratories Inc
1219 Glen Rock Avenue
Waukegan
IL 60085
Tel: +1 847 623 0370
Fax: +1 847 623 9173
E-mail: pfanstiehl-info@ferro.com
Web: www.ferro.com

Fisher Scientific
2000 Park Lane
Pittsburgh
PA 15275
Tel: +1 800 766 7000
Fax: +1 800 926 1166
Web: www.fishersci.com

FMC Biopolymer
1735 Market Street
Philadelphia
PA 19103
Tel: +1 800 526 3649
Fax: +1 215 299 6291
E-mail: pharm_info@fmc.com
Web: www.fmcbiopolymer.com
Trade names: *Ac-Di-Sol; Aquacoat cPD; Aquacoat ECD; Avicel PH; Celphere; Gelcarin; Marine Colloids; Protacid; Protanal; SeaSpen PF; Viscarin;.*

Foremost Farms USA
E10889A Penny Lane
PO Box 111
Baraboo
WI 53913 0111
Tel: +1 800 362 9196
Fax: +1 608 356 9005
E-mail: commdept@foremostfarms.com
Web: www.foremostfarms.com

Fuji Chemical Industries Health Science (USA) Inc
7B Marlen Drive
Robbinsville
NJ 08691
Tel: +1 856 234 3636
Fax: +1 856 778 2297
E-mail: contact@fcihealthscience.com
Web: www.fcihealthscience.com
Trade names: *Fujicalin; Neusilin.*

Fuji Chemical Industries (USA) Inc *see* Fuji Chemical Industries Health Science (USA) Inc

Gallard-Schlesinger Industries Inc
245 Newtown Road
Suite 305
Palinview
NY 11803
Tel: +1 516 683 6900
Fax: +1 516 683 6990
E-mail: info@gallard.com
Web: www.gallard-schlesinger.com

Gattefossé Corp
650 From Road
Paramus
NJ 07652
Tel: +1 201 265 4800
Fax: +1 201 265 4853
E-mail: info@gattefossecorp.com
Web: www.gattefossecorp.com
Trade names: *Compritol 888 ATO; Labrafac CC; Precirol ATO 5.*

Generichem Corp
PO Box 457
Totowa
NJ 07511-0457
Tel: +1 973 256 9266
Fax: +1 973 256 0069
E-mail: info@generichem.com
Web: www.generichem.com
Trade names: *Prejel; Primellose; Primogran W; Primojel.*

George Uhe Co Inc
12 Route 17 North
PO Box 970
Paramus
NJ 07653 0970
Tel: +1 800 850 4075
Fax: +1 201 843 7517
E-mail: global@uhe.com
Web: www.uhe.com

Grain Processing Corp
1600 Oregon Street
Muscatine
IA 52761
Tel: +1 563 264 4265
Fax: +1 563 264 4289
E-mail: sales@grainprocessing.com
Web: www.varied.com
Trade names: *Instant Pure-Cote; Maltrin; Maltrin QD; Pure-Bind; Pure-Cote; Pure-Dent; Pure-Dent B851; Pure-Gel; Pure-Set; Spress B820.*

GR O'Shea Company
650 East Devon Avenue
Suite 180
Itasca
IL 60143-3142
Tel: +1 630 773 3223
Fax: +1 630 773 3553
E-mail: general@groshea.com
Web: www.groshea.com
Trade names: *Castorwax; Castorwax MP 70; Castorwax MP 80.*

Hawkins Chemical Inc
Pharmaceutical Group
3100 East Hennepin Avenue
Minneapolis
MN 55413
Tel: +1 612 331 6910
Fax: +1 612 331 5304
Web: www.hawkinschemical.com

Helm New York Inc
1110 Centennial Avenue
Piscataway
NJ 08854-4169
Tel: +1 732 981 1160
Fax: +1 732 981 0965
E-mail: info@helmnewyork.com
Web: www.helmnewyork.com

Hercules Inc *see* Aqualon

Huntsman Tioxide *see* Tioxide Americas Inc

ICI Surfactants
PO Box 8340
Wilmington
DE 19803 8340
Tel: +1 302 887 5739
Fax: +1 302 887 3525
Web: www.ici.com
Trade names: *Brij.*

Inolex Chemical Co
Jackson & Swanson Streets
Philadelphia
PA 19148 3497
Tel: +1 215 271 0800
Fax: +1 215 271 2621
E-mail: cheminfo@inolex.com
Web: http://www.inolex.com
Trade names: *Lexalt L; Lexgard B; Lexol IPP-NF.*

International Fiber Corporation
50 Bridge Street
North Tonawanda
NY 14120
Tel: +1 716 693 4040
Fax: +1 716 693 3528
E-mail: ifc@ifcfiber.com
Web: http://www.ifcfiber.com
Trade names: *Solka-Floc.*

International Specialty Products
1361 Alps Road
Wayne
NJ 07470
Tel: +1 973 628 4000
Fax: +1 973 872 1583
E-mail: info@ispcorp.com
Web: www.ispcorp.com
Trade names: *Celex; Germall 115; Kelacid; Kelcosol; Keltone; Pharmasolve; Plasdone; Plasdone S-630; Polyplasdone XL; Polyplasdone XL-10.*

ISP *see* International Specialty Products

Jarchem Industries Inc
414 Wilson Avenue
Newark
NJ 07105
Tel: +1 973 344 0600
Fax: +1 973 344 5743
E-mail: info@jarchem.com
Web: www.jarchem.com
Trade names: *Jarcol 1-20.*

Jeen International Corp
24 Madison Road
Fairfield
NJ 07004
Tel: +1 800 771 5336
Fax: +1 973 439 1402
E-mail: info@jeen.com
Web: www.jeen.com
Trade names: *Jeechem.*

J Rettenmaier USA *see* JRS Pharma LP

JRS Pharma LP
2981 Route 22, Suite 1
Patterson
NY 12563
Tel: +1 845 878 3414
Fax: +1 845 878 3484
E-mail: sales@jrspharma.com
Web: www.jrspharma.com
Trade names: *Arbocel; Candex; Compactrol; Emcocel; Emcompress; Emcompress Anhydrous; Emdex; Explotab; Lubritab; ProSolv; Pruv; Satialgine H8; Vivapress Ca; Vivapur; Vivasol; Vivastar P.*

JT Baker Inc
Mallinkrodt Baker Inc
222 Red School Lane
Phillipsburg
NJ 08865
Tel: +1 908 859 2151
Fax: +1 908 859 6905
E-mail: infombi2@tycohealthcare.com
Web: www.jtbaker.com
Trade names: *HyQual.*

Jungbunzlauer Inc
7 Wells Avenue
Newton Centre
MA 02459
Tel: +1 617 969 0900
Fax: +1 617 964 3007
Web: www.jungbunzlauer.com
Trade names: *Citrofol AI.*

KIC Chemicals Inc
84 Business Park drive
Armonk
NY 10504
Tel: +1 914 273 6555
Fax: +1 914 273 6760
E-mail: Sales@KICgroup.com
Web: www.kicgroup.com

Koster Keunen LLC
1021 Echo Lake Road
PO Box 69
Watertown
CT 06795
Tel: +1 860 945 3333
Fax: +1 860 945 0330
E-mail: info@kosterkeunen.com
Web: www.kosterkeunen.com
Trade names: *Permulgin D.*

Kraft Chemical Co
1975 N Hawthorne Avenue
Melrose Park
IL 60160
Tel: +1 800 345 5200
Fax: +1 708 345 4005
E-mail: kraftchem@aol.com
Web: www.kraftchemical.com

Lanxess Corp
111, RIDC Park West Drive
Pittsburg
PA 15275-1112
Tel: +1 412 809 1000
Web: www.lanxess.com;
www.bayferrox.com
Trade names: *Bayferrox 306; Bayferrox 920Z.*

Lipo Chemicals Inc
207 19th Avenue
Paterson
NJ 07504
Tel: +1 973 345 8600
Fax: +1 973 345 8365
E-mail:
salesandmarketing@lipochemicals.com
Web: www.lipochemicals.com
Trade names: *Lipo GMS 410; Lipo GMS 450; Lipo GMS 600; Lipocol; Lipocol C; Lipolan; Liponate IPP; Lipovol CAN; Lipovol SES; Uniphen P-23.*

Lipscomb Chemical Company Inc
4401 Atlantic Ave
Suite 410
Long Beach
CA 90807
Tel: +1 562 728 6321
Fax: +1 562 728 9170
E-mail: scrawford@lipscombchemical.com
Web: www.lipscombchemical.com

Loos & Dilworth Inc
61 East Green Lane
Bristol
PA 19007
Tel: +1 215 785 3591
Fax: +1 215 785 3597
E-mail: dtompkins@loosanddilworth.com
Web: www.loosanddilworth.com
Trade names: *Pamolyn.*

Lucas Meyer Inc
PO Box 3218
Decatur
IL 62524 3218
Tel: +1 217 8753660
Fax: +1 217 8775046
E-mail: lecithin@midwest.net
Web: www.lucas-meyer.com

Luzenac America
345 Inverness Drive South
Suite 310
Centennial
CO 80112
Tel: +1 303 643 0400
Fax: +1 303 643 0444
Web: www.luzenac.com
Trade names: *Altalc.*

Lyondell Chemical Co
PO Box 3646
Houston
TX 77253 3646
Tel: +1 713 652 7200
Web: www.lyondell.com

Mantrose Bradshaw Zinsser Group *see* Mantrose-Haeuser Co Inc

Mantrose-Haeuser Co Inc
1175 Post Road East
Westport
CT 06880
Tel: +1 203 454 1800
Fax: +1 203 227 0558
E-mail: susan.coleman@mantrose.com
Web: www.mbzgroup.com
Trade names: *CertiSeal; Mantrolac R-49.*

McNeil Nutritionals LLC
McNeil Specialty Products Co
501 George Street
PO Box 2400
New Brunswick
NJ 0891 1161
Tel: +1 732 524 6704
Fax: +1 732 247 7482
Web: www.splenda.com
Trade names: *Splenda.*

Mendell *see* Penwest Pharmaceuticals Co

Merisant
10 South Riverside Plaza
Suite 850
Chicago
IL 60606
Tel: +1 312 840 6000
Fax: +1 312 840 5400
Web: www.merisant.com
Trade names: *Canderel; Equal; NutraSweet.*

M Michel and Company Inc
PO Box 788
Planetarium Station
New York
NY 10024 0545
Tel: +1 212 344 3878
Fax: +1 212 344 3880
Web: www.mmichel.com
Trade names: *Cachalot.*

Morflex Inc
2110 High Point Road
Greensboro
NC 27403 2642
Tel: +1 336 292 1781
Fax: +1 336 854 4058
E-mail: skennedy@morflex.com
Web: www.morflex.com
Trade names: *Citroflex 4; Citroflex A-2; Citroflex A-4.*

Mutchler Inc
20 Elm Street
Harrington Park
NJ 07640
Tel: +1 201 768 1100
Fax: +1 201 768 9960
E-mail: info@mutchlerchem.com
Web: www.mutchlerchem.com

Napp Technologies Inc
401 Hackensack Ave
Hackensack
NJ 0760
Tel: +1 201 843 4664
Fax: +1 201 843 4737
Web: www.napptech.com

National Starch & Chemical Co
742 Grayson Street
Berkeley
CA 94710 2677
Tel: +1 510 548 6722
Fax: +1 510 841 3150
E-mail: nscinquiry@adh.com
Web: www.nationalstarch.com
Trade names: *National 78-1551; Purity 21; Purity 826; Unipure WG220.*

Nipa Laboratories Inc
(Clariant Corporation)
625 East Catawba Avenue
Mount Holly
NC 28210
Tel: +1 973 334 9227
Fax: +1 704 822 2241
Trade names: *Nipacide PX; Propyl parasept.*

Nippon Soda Co Ltd
Nisso America Inc
220 East 42nd Street
Suite 3002
New York
NY 10017
Tel: +1 212 490 0350, 0351
Fax: +1 212 972 9361
Web: www.nippon-soda.co.jp
Trade names: *Nisso HPC.*

Noveon Inc
9911 Brecksville Road
Cleveland
OH 44141-3247
Tel: +1 216 447 5000
Web: www.noveoninc.com
Trade names: *Carbopol; Noveon AA-1; Pemulen; Protachem; Protachem IPP.*

NutraSweet Company, The *see* Merisant

Nutrinova Inc
285 Davidson Avenue
Suite 102
Somerset
NJ 08873
Tel: +1 800 786 3883
Fax: +1 732 271 7235
Trade names: *Sunett.*

O'Shea Company *see* GR O'Shea Company

Paddock Laboratories Inc
3940 Quebec Avenue North
Minneapolis
MN 55429
Tel: +1 763 546 4676
Fax: +1 763 546 4676
E-mail: info@paddocklabs.com
Web: www.paddocklabs.com

Particle Dynamics Inc
KV Pharmaceutical Co
2601 South Hanley Road
Saint Louis
MO 63144
Tel: +1 314 968 2376
Fax: +1 314 968 5208
E-mail: info@particledynamics.com
Web: www.particledynamics.com
Trade names: *Destab; Tablitz.*

Penta Manufacturing Co
50 Okner Parkway
Livingston
NJ 07039-1604
Tel: +1 973 740 2300
Fax: +1 973 740 1839
E-mail: sales@pentamfg.com
Web: www.pentamfg.com

Penwest Pharmaceuticals Co *see* JRS Pharma LP

Pfaltz & Bauer
172 E. Aurora St
Waterbury
CT 06708
Tel: +1 203 574 0075
Fax: +1 203 574 3181
E-mail: sales@pfaltzandbauer.com
Web: www.pfaltzandbauer.com
Trade names: *Garantose.*

Pfanstiehl Laboratories Inc *see* Ferro Pfanstiehl Laboratories Inc

Pfizer Corp
235 East 42nd Street
New York
NY 10017 5755
Tel: +1 212 573 2323
Fax: +1 212 573 7851
E-mail: info@pfizer.com
Web: www.pfizer.com

PMC Specialities Group Inc
501 Murray Road
Cincinnati
OH 45217
Tel: +1 800 543 2466
Fax: +1 513 482 7373
Web: www.pmcsg.com

Pokonobe Industries Inc
PO Box 1756
Santa Monica
CA 90406
Tel: +1 310 392 1259
Fax: +1 310 392 3659
E-mail: info@pokonobe.com
Web: www.pokonobe.com

Polysciences Inc
400 Valley Road
Warrington
PA 18976
Tel: +1 800 523 2575
Fax: +1 800 343 3291
E-mail: info@polysciences.com
Web: www.polysciences.com

Premium Ingredients Ltd
285 East Fullerton Avenue
Carol Stream
IL 60188
Tel: +1 630 868 0380
Fax: +1 630 868 0390
E-mail: sales@premiumingredients.com
Web: www.premiumingredients.com

Protameen Chemicals
375 Minnisink Road
Totowa
NJ 07511
Tel: +1 973 256 4374
Fax: +1 973 256 6764
E-mail: info@protameen.com
Web: www.protameen.com
Trade names: *Procol; Protachem; Protachem GMS-450; Protachem IPP; Protalan anhydrous; Protalan M-16; Protalan M-26.*

Purac America Inc
111 Barclay Boulevard
Lincolnshire Corporate Center
Lincolnshire
IL 60069
Tel: +1 847 634 6330
Fax: +1 847 634 1992
E-mail: pam@purac.com
Web: www.purac.com
Trade names: *Lacty; Purac 88 PH; Pursasorb; Purasorb PD; Pursasorb PDL; Pursasorb PDLG; Purasorb PG; Purasorb PL.*

Reade Advanced Materials Inc
Post Office Drawer 15039
3708 Pawtucket Avenue
Providence
RI 02915-0039
Tel: +1 401 433 7000
Fax: + 401 433 7001
E-mail: sales.east@reade.com
Web: www.reade.com

Reheis Inc
235 Snyder Ave
Berkeley Heights
NJ 07922
Tel: +1 908 464 1500
Fax: +1 908 464 7726
Web: www.reheis.com
Trade names: *Rehydraphos.*

Reilly Industries Inc
300 N Meridian Street
Indianapolis
IN 46204-1763
Tel: +1 317 247 8141
Fax: +1 317 248 6472
E-mail: webmaster@reillyind.com
Web: www.reillyind.com
Trade names: *Citroflex 2.*

Rennecker Ltd
Cleveland
Ohio
Tel: +1 330 225 2326
Fax: +1 330 225 1542
E-mail: sales@renneckerltd.com
Web: www.renneckerltd.com
Trade names: *Hectabrite AW; Hectabrite DP.*

Research Diagnostics Inc
Pleasant Hill Road
Flanders
NJ 07836
Tel: +1 973 584 7093
Fax: +1 973 584 0210
E-mail: sales@researchd.com
Web: www.researchd.com
Trade names: *Encapsin.*

Rettenmaier *see* JRS Pharma LP

RFI Ingredients
300 Corporate Drive, Suite 14
Blauvelt
NY 10913
Tel: +1 845 358 8600
Fax: +1 845 358 9003
E-mail: rfi@rfiingredients.com
Web: www.rfiingredients.com
Trade names: *Talin.*

Rhodia Inc *see* Rhodia Pharma Solutions Inc

Rhodia Pharma Solutions Inc
259 Prospect Plains Road
CN 7500
Cranbury
NJ 08512 7500
Tel: +1 888 776 7337
Fax: +1 609 860 0344
Web: www.rhodia-pharmasolutions.com
Trade names: *A-TAB; DI-TAB; Meyprodor; Meyprofin; Meyprofleur; Meyprogat; Rhodiarome; Rhodigel; Rhovanil; TRI-CAL WG; TRI-TAB.*

RIA International
9 Whippany Road
#C3
Whippany
NJ 07981
Tel: +1 973 581 1282
Fax: +1 973 581 1283
E-mail: ria@riausa.com
Web: www.riausa.com

Rita Corp
PO Box 457
850 South Rt. 31
Crystal Lake
IL 60014-0457
Tel: +1 815 337 2500
Fax: +1 815 337 2522
E-mail: info@ritacorp.com
Web: www.ritacorp.com
Trade names: *Acritamer; Forlan 500; Patlac LA; Rita CA; Rita GMS; RITA HA C-1-C; Rita IPM; Rita SA; Ritaceti; Ritachol 2000; Ritawax; Ritoleth; Ritox; Tealan.*

Rohm America Inc
2 Turner Place
PO Box 365
Piscataway
NJ 08855
Tel: +1 877 764 6872
Fax: +1 732 981 5484
Web: www.rohmamerica.com
Trade names: *Eudragit.*

Rohm and Haas Co
100 Independence Mall West
Philadelphia
PA 19106 2399
Tel: +1 215 592 3000
Fax: +1 219 592 3377
Web: www.rohmhaas.com
Trade names: *Amberlite IRP-88.*

Roquette America Inc
1417 Exchange Street
PO Box 6647
Keokuk
IA 52632-6647
Tel: +1 319 524 5757
Fax: +1 319 526 2345
E-mail: roquette.jur@wanadoo.fr
Web: www.roquette.com
Trade names: *Flolys; Fluidamid R444P; Glucidex; Keoflo ADP; Kleptose; Lycadex PF; Lycasin 80/55; Lycasin HBC; Lycatab C; Lycatab DSH; Lycatab PGS; Maltisorb; Maltisorb 75/75; Neosorb; Pearlitol; Roclys; Roferose; Xylisorb.*

RT Vanderbilt Company Inc
30 Winfield Street
PO Box 5150
Norwalk
CT 06856-5150
Tel: +1 800 243 6064
Fax: +1 203 853 1452
Web: www.rtvanderbilt.com
Trade names: *Vanzan NF; Veegum.*

Ruger Chemical Co Inc
1515 West Blancke Street
Linden
NJ 07036
Tel: +1 973 926 0331
Fax: +1 973 926 4921
Web: www.rugerchemical.com

Sanofi-Synthelabo Inc
90 Park Avenue
New York
NY 10016
Tel: +1 212 551 400
Web: www.sanofi-synthelabous.com
Trade names: *Zephiran.*

Sasol North America Inc
900 Threadneedle
Suite 100
Houston
TX 77079-2990
Tel: +1 281 588 3000
Fax: +1 281 588 3144
E-mail: info@us.sasol.com
Web: www.sasolCustomer1.com
Trade names: *Imwitor 191; Imwitor 900; Lipoxol.*

Scandinavian Formulas Inc
140 East Church St
Sellersville
PA 18960
Tel: +1 215 453 2507
Fax: +1 215 257 9781
E-mail: info@scandinavianformulas.com
Web: www.scandinavianformulas.com

Seidler Chemical Company
537 Raymond Blvd
Newark
NJ 07105
Tel: +1 973 465 1122
Fax: +1 973 465 4469
E-mail: sales@sedielerchem.com
Web: www.seidlerchem.com

Seltzer Chemicals Inc
5927 Geiger Court
Carlsbad
CA 92008-7305
Tel: +1 800 735 8137
Fax: +1 760 438 0336
Web: www.seltzerchemicals.com

Sensus America LLC
Princeton Coporate Plaza
1 Deer Park Drive
Suite J
Manmouth Junction
NJ 08852
Tel: +1 646 452 6140
Fax: +1 646 452 6150
E-mail: contact@sensus.us
Web: www.sensus.us
Trade names: *Frutafit.*

Sigma-Aldrich Corp
PO Box 14508
Saint Louis
MO 63178
Tel: +1 314 771 5765
Fax: +1 314 771 5757
E-mail: OC_DOM_HC@sial.com
Web: www.sigmaaldrich.com
Trade names: *Kodaflex DBS; Thimerosal Sigmaultra.*

Spectrum Quality Products Inc
14422 South San Pedro Street
Gardena
CA 90248 2027
Tel: +1 800 813 1514
Fax: +1 800 525 2299
E-mail: sales@spectrumchemical.com
Web: www.spectrumchemical.com

SPI Pharma Group
SPI Polyols, Inc
321 Cherry Lane
New Castle
DE 19720 2780
Tel: +1 302 576 8554
Fax: +1 302 576 8569
Web: www.spipharma.com
Trade names: *Advantose 100; Advantose FS 95; Effer-Soda; Maltisweet 3145; Mannogem; Sorbogem; Sunmalt; Sunmalt S.*

Staley Mfg Co *see* Tate & Lyle

Stepan Co
22 West Frontage Road
Northfield
IL 60093
Tel: +1 847 446 7500
Fax: +1 847 501 2100
Trade names: *Kessco CA; Kessco EO; Kessco GMO; Kessco GMS; Kessco IPP; Stepan GMO; Stepan GMS; Stepan IPM; Stepan IPP; Wecobee.*

Strahl & Pitsch Inc
230 Great East Neck Road
West Babylon
NY 11704
Tel: +1 631 587 9000
Fax: +1 631 587 9120
E-mail: info@strahlpitsch.com
Web: www.spwax.com

Takeda Pharmaceuticals North America Inc
475 Half Day Road
Suite 500
Lincolnshire
IL 60069
Tel: +1 847 383 3000
Web: www.takedapharm.com

Tate & Lyle
Cerel Sweeteners
2200 E Eldorado Street
PO Box 151
Decatur
IL 62526
Tel: +1 800 526 5728
Fax: +1 217 421 3167
Web: www.tateandlyle.com
Trade names: *Di-Pac; Krystar; Star-Dri.*

Thomas Scientific
PO Box 99
Swedesboro
NJ 08085
Tel: +1 856 467 2000
Fax: +1 856 467 3087
E-mail: value@thomassci.com
Web: www.thomassci.com

Thornley Company
Suite 204 1500
East Newport Pike
Wilmington
DE 19804 2346
Tel: +1 302 933 8300
Fax: +1 302 933 8308
E-mail: Murphy@Thornleycompany.com
Web: www.thornleycompany.com
Trade names: *Liponic 70-NC; Liponic 76-NC.*

TIC Gums
4609 Richlynn Drive
PO Box 369
Belcamp
MD 21017
Tel: +1 410 273 7300
Fax: +1 410 273 6469
E-mail: svandenheuvel@ticgums.com
Web: www.ticgums.com

Tioxide Americas Inc
(Huntsman Tioxide)
4575 Weaver Parkway
Warrenville
IL 60555
Tel: +1 630 836 2400
Fax: +1 630 836 2480
Web: www.huntsman.com
Trade names: *Tioxide.*

Triple Crown America
13 North Seventh Street
Perkasie
PA 18944
Tel: +1 215 453 2500
Fax: +1 215 453 2508
E-mail: info@triplecrownamerica.com
Web: www.triplecrownamerica.com

Universal Preserv-A-Chem Inc
33, Truman Drive South
Edison
NJ 08817-2426
Tel: +1 732 777 7338
Fax: +1 732 777 7885
Web: www.upichem.com

Vanderbilt Company Inc *see* RT Vanderbilt Company Inc

Van Waters and Rogers Inc *see* Vopak USA Inc

Virginia Dare
882 Third Avenue
Brooklyn
NY 11232
Tel: +1 718 788 1776
Fax: +1 718 768 3978
E-mail: webinfo@virginiadare.com
Web: www.virginiadare.com

Voigt Global Distribution LLC
PO Box 412762
Kansas City
MO 64141-2762
Tel: +1 877 484 3552
Fax: +1 816 471 9502

Vopak USA Inc
2000 West Loop South
Suite 2200
Houston
TX 77027
Tel: +1 713 561 7200
Fax: +1 713 561 7322
E-mail: Jackie.gault@vopak.com

Wacker Biochem Corp *see* Wacker Chemical Corp

Wacker Chemical Corp
1 Wacker Drive
Eddyville
IA 52553
Tel: +1 515 969 4817
Fax: +1 515 969 4929
E-mail: info.finechemicals@wacker.com
Web: www.wacker-biochem.com
Trade names: *Cavamax W6 Pharma; Cavamax W7 Pharma; Cavamax W8 Pharma; Wacker HDK.*

Warner Jenkinson Pharmaceutical
107 Wade Avenue
PO Box 705
South Plainfield
NJ 07080 1311
Tel: +1 908 757 4500
Fax: +1 908 757 3170
E-mail: wje@aes.co.uk

Welch, Holme & Clark Co Inc
7 Avenue L
Newark
NJ 07105
Tel: +1 973 465 1200
Fax: +1 973 465 7332
Web: www.welch-holme-clark.com

Whittaker Clark, and Daniels Inc
1000 Coolidge St
S. Plainfield
NJ 07080
Tel: +1 908 561 6100
Fax: +1 800 833 8139
E-mail: customerservice@wcdinc.com
Web: www.wcdinc.com
Trade names: *Albagel.*

Witco Corp *see* Crompton Corp

Zhong Ya Chemical (USA) Ltd
50 Colonial Drive
Piscataway
NJ 08854
Tel: +1 732 981 9288
Fax: +1 732 981 9488
E-mail: sales@zhongyachemical.com
Web: www.zhongyachemical.com

ZLB Behring
1020 First Avenue
PO Box 61501
King of Prussia
PA 19406 0901
Web: www.zlbbehring.com

Suppliers List: Others

Aastrid International
247-248 Udyog Bhavan
Sonawala Lane
Goregaon East
Mumbai 400 063
India
Tel: +91 22 5691 4333
Fax: +91 22 5691 4334
E-mail: aastrid@vsnl.com
Web: www.aastrid.com

Ajinomoto Co Inc
15-1, Kyobashi
1-chome, Chuo-ku
Tokyo 104-8315
Japan
Tel: +81 (3)5250 8111
E-mail: g-webmaster@ajinimoto.com
Web: www.ajinomoto.com
Trade names: *Pal Sweet; Pal Sweet Diet.*

Asahi Kasei Corporation
Hibiya-Mitsui Building
Functional Additives Division
1-2 Yuraku-cho 1-Chome
Chiyoda-ku
Tokyo 100-8440
Japan
Tel: +81 3 3507 2060
Fax: +81 3 3507 2495
Web: www.asahi-kasei.co.jp
Trade names: *Celphere; Ceolus KG.*

Cerestar Jiliang Maize Industry Co Ltd
Songyuan
Jianguan Industry Development Zone
138006 Songyuan Jilin Province
China
Tel: +86 (0)438 2180 812
Fax: +86 (0)438 2180 813
E-mail: cjmicom@mail.jl.cn
Web: www.cargillchina.com

Charles Tennant & Co (Canada) Ltd
34 Clayson Road
Toronto
ON M9M 2G8
Canada
Tel: +1 416 741 9264
Fax: +1 416 741 6642
Web: www.ctc.ca
Trade names: *Jeecol ODD.*

Choice Korea Co
207 Shin Song Plaza 1423-2
Kwanyang-1 Dong
Donan-Ku
Anyang City
Kyunggi-do
Korea
Tel: +82 314 240 212
Fax: +82 314 240 213
E-mail: choice4@kornet.net
Web: www.choicekorea.com
Trade names: *Waglinol 6016.*

Cosmos Chemical Co Ltd
506 Jianda Building
223 North Zhongshan Road
Nanjing 210009
China
Tel: +86 25 3346885
Fax: +86 25 3346877
E-mail: cosmos@cosmoschem.com
Web: cosmoschem.com

EPS Impex Co
PO Box 21904
Damai Plaza Luyang
88777 Kota Kinabalu
Malaysia
Tel: +60 88 316470
Fax: +60 88 316741
E-mail: patwary@streamyx.com
Web: www.epsimpex.com

Fine Chemicals Corporation (Pty) Ltd
PO Box 253
Eppindust 7475
South Africa
Tel: +27 21 531 6421
Fax: +27 21 531 1458
E-mail: maske@iafrica.com

Fuji Chemical Industry Co Ltd
55 Yokohoonji
Kamiichi-machi
Nakanikawa-gun
Toyama 930-0397
Japan
Tel: +81 764 72 2323
Fax: +81 764 72 5539
E-mail: info@fujichemical.co.jp
Web: www.fujichemical.co.jp
Trade names: *Fujicalin; Neusilin.*

Gadot Petrochemical Industries Ltd
16 Habonim Street
Netanya South Industrial Zone
42504 Israel
Israel
Tel: +972 9 892 9530
Fax: +972 9 865 3385
E-mail: gsales@gadot.com
Web: www.gadot.com

Glide Chem Pvt Ltd
Corporate Office
S-39 Rajouri Garden
New Delhi 110027
India
Tel: +91 11 514 43531
Fax: +91 11 511 1752/591 1962
E-mail: glide@bol.net.in
Web: www.glideindia.com

Hayashibara Co Ltd
1-2-3 Shimoishii
Okayama
700-0907
Japan
Tel: +81 86 224 4311
Fax: +81 86 222 8942
Web: www.hayashibara.co.jp
Trade names: *Maltose HH.*

Henley Chemicals
199 Courtland Avenue
Concord
Ontario
L4K 4T2
Canada
Tel: +1 416 661 1500
Web: www.henleychem.com
Trade names: *Tego Alkanol 1618; Tego Alkanol 6855.*

Highland International
25 Kembrose Estate
Off Lbs Marg, Bhandup
Mumbai 400 078
India
Tel: +91 22 256 50529
Fax: +91 22 264 81356
Web: www.indiamart.com/
highland-international

Jiangxi Mosashino Co Ltd
Xiaolan Industry Park of Nanchang
Jiangxi 330200
China
Tel: +86 791 576 1066
Fax: +86 791 576 1063
E-mail: admini@china-musashino.com
Web: www.china-musashino.com

Kibun Food Chemifa Co Ltd
2-12-11 Minato
Chuo-ku
Tokyo 104
Japan
Tel: +81 3 3206 0776
Fax: +81 3 3206 0788
E-mail: webmaster@kibunfc.co.jp
Web: www.kibunfc.co.jp

Lactose New Zealand
PO Box 424
Hawera
New Zealand
Tel: +64 6 274 8869
Fax: +64 6 274 8927
E-mail: marketing@lactose.co.nz
Web: www.lactose.co.nz
Trade names: *Wyndale.*

LS Raw Materials Ltd
Harav Kook
30/3 Petach Tikvah
49315
Israel
Tel: 972 3 922 3966
Fax: 972 3 921 2647
E-mail: info@ls-rawmaterials.com
Web: www.ls-rawmaterials.com

Mitsubishi-Kagaku Foods Corporation
1-3-9 Ginza
Chuo-ku
Tokyo 104
Japan
Tel: +81 3 3563 1514
Fax: +81 3 3563 1676
Web: www.mfc.co.jp

Nikko Chemicals Co Ltd
Nikko Chemicals Co Ltd
Chuo-ku
Tokyo 103-0002
Japan
Tel: +81 3 3661 1677
Fax: +81 3 3664 8620
E-mail: info@nikkol.co.jp
Web: www.nikkol.co.jp
Trade names: *Nikkol.*

Nippon Soda Co Ltd
2-1 Otemachi 2-chome
Chiyoda-ku Tokyo
100-8165
Japan
Tel: +81 3324 56054
Fax: +81 3324 56238
Web: www.nippon-soda.co.jp
Trade names: *Nisso HPC.*

Pachem Distributions Inc
1800 Boulevard
Michelin
Laval (Québec)
H7L 4R3
Canada
Tel: +1 450 682 4044
Fax: +1 450 682 2044
E-mail: service@pachemdistribution.com
Web: www.pachemdistribution.com
Trade names: *Emerest 2316.*

Raw Materials Ltd *see* LS Raw Materials Ltd

San Fu Chemical Company Ltd
Rm 1704, 17/F
Greenfield Tower
Concordia Plaza
1, Science Museum Road TST
Kowloon, Hong Kong
China
Tel: +1 852 2609 1138
Fax: +1 852 2609 0731
E-mail: info@fangda.com.hk
Web: www.cyclamate.com

Sarman Industries
A-37 Gandhi Nagar
Moradabad 244001
India
Tel: +91 591 249 3544
Fax: +91 591 249 3544
E-mail: sahaj1@sancharnet.in
Web: www.indiamart.com/
sarmanindustries

Shangyuchem
Biochem Division
Sanpeng Bridge
Baiguan
Shangyu 312351
China
Tel: +86 575 2210376
Fax: +86 575 2129555
E-mail: sales@shangyuchem.com
Web: www.biochemicals.cn

Shijiazhuang Pharmaceutical Group Co Ltd
276 Zhongshan West Road
Shijiazhuang
China
Tel: +86 311 7037015
Fax: +86 311 7039608
E-mail: zhangiv@mail.ecspc.com
Web: www.e-cspc.com

Shin-Etsu Chemical Co Ltd
Cellulose and Pharmaceutical Excipients
Asahi-Tokai Building
Department 6-1, Ohtemachi 2-chrome
Chiyoda-ku
Tokyo
Japan
Tel: +81 3 3246 5261
Fax: +81 3 3246 5372
Web: www.shinetsu.co.jp
Trade names: *Aqoat; Aqoat AS-HF/HG; Aqoat AS-LF/LG; Aqoat AS-MF/MG; Metolose.*

Sumitomo Chemical
27-1 Shinkawa 2-chome
Chuo-ku
Tokyo 104-8260
Japan
Tel: + 81-3-5543-5500
Fax: + 81-3-5543-5901
Web: www.sumitomo-chem.co.jp

Takeda Chemical Industries Ltd *see*
Takeda Pharmaceutical Company ltd

Takeda Pharmaceutical Company Ltd
1-1 Doshomachi 4-chrome
Chuo-ku
Osaka 540 8645
Japan
Tel: +81 6 6204 2111
Fax: +81 6 6204 2880
Web: www.takeda.co.jp

Univar Canada Ltd
9800 Van Horne Way
Richmond
BC V6X 1W5
Canada
Tel: +1 604 273 1441
Fax: +1 604 273 2046
E-mail: webmaster@univarcanada.com
Web: www.univarcanada.com

Wintersun Chemical
3100 East Cedar Street
Suite #15
Ontario 91761
Canada
Tel: +1 909 930 1688
Fax: +1 909 947 1788
E-mail: sales@wintersunchem.com
Web: www.wintersunchem.com

Wuxi Dazhong Chemical Industry Co Ltd
81 Yehuayan
Guangrui Road
Wuxi City 214 011
China
Tel: +86 510 244 9082
Fax: +86 510 244 9082z

Xiamen Topusing Chemical Co Ltd
7/H Chang An Building
Lvling Road
Jiangtou
Xiamen 361 009
China
Tel: +86 592 553 8032
Fax: +86 592 553 8092
E-mail: tuchem@public.xm.fj.cn
Web: www.topusing.com

Xinchem Co
401/17, 3455 Chunshen Road
Shanghai 201100
China
Tel: +86 21 34123252
Fax: +86 21 54153973
E-mail: info@finechemnet.com
Web: www.finechemnet.com

Yee Young Cerachem Ltd
Room 1506
Chungho Building
51–2 Pangi 2-Dong
Songpa-Ku
Seoul
South Korea
Tel: +82 24 200 331
Fax: +82 24 241 877
E-mail: khchang@yeeyoung.co.kr
Web: www.yeeyoung.co.kr
Trade names: *Pentonium.*

Appendix II: List of Excipient ‘E’ Numbers

E Number	*Excipient*	
E100	Curcumin	192
E101	Riboflavin	192
E102	Tartrazine	192, 198
E104	Quinoline Yellow	192
E110	Sunset Yellow FCF	192, 198
E120	Carmine	192
E122	Carmoisine	192
E123	Amaranth	192
E124	Ponceau 4R	192
E127	Erythrosine	192
E129	Allura Red AC	192
E131	Patent Blue V	192
E132	Indigo Carmine	192, 197
E133	Brilliant Blue FCF	192
E140	Chlorophylls	192
E141	Copper Complexes of Chlorophylls and Chlorophyllins	192
E142	Green S	192
E150	Caramel	192
E151	Brilliant Black BN	192
E153	Vegetable Carbon	192
E160	Carotenoids, Alpha-, Beta-, Gamma-carotene	192
E160	Carotenoids, Beta-apo-8′ Carotenal	192
E160	Carotenoids, Capsanthin	192
E160	Carotenoids, Capsorubin	192
E160	Carotenoids, Ethyl Ester of Beta-apo-8′ Carotenoic Acid	192
E160	Carotenoids, Lycopene	192
E160a	Beta-carotene	196
E161	Xanthophylls, Canthaxanthin	192
E161	Xanthophylls, Lutein	192
E162	Beetroot Red	192
E163	Anthocyanins, Cyanidin	192
E163	Anthocyanins, Delphidin	192
E163	Anthocyanins, Malvidin	192
E163	Anthocyanins, Pelargonidin	192
E163	Anthocyanins, Peonidin	192
E163	Anthocyanins, Petunidin	192
E170	Calcium Carbonate	89, 192
E171	Titanium Dioxide	192, 782
E172	Iron Oxides	364
E172	Iron Oxides and Hydroxides	192
E173	Aluminum	192
E200	Sorbic Acid	710
E201	Sodium Sorbate	712
E202	Potassium Sorbate	609
E203	Calcium Sorbate	712
E210	Benzoic Acid	66
E211	Sodium Benzoate	662
E212	Potassium Benzoate	596
E214	Ethylparaben	287
E215	Ethylparaben Sodium	289
E216	Propylparaben	629
E217	Propylparaben Sodium	631
E218	Methylparaben	466
E219	Methylparaben Sodium	469

E Number	*Excipient*	
E221	Sodium Sulfite	708
E222	Sodium Bisulfite	691
E223	Sodium Metabisulfite	690
E224	Potassium Metabisulfite	607
E228	Potassium Bisulfite	608
E260	Acetic Acid, Glacial	6
E262	Sodium Acetate	654
E270	Lactic Acid	381
E280	Propionic Acid	617
E281	Sodium Propionate	699
E281	Anhydrous Sodium Propionate	700
E281	Sodium Propionate	699
E282	Calcium Propionate	700
E283	Potassium Propionate	700
E284	Boric Acid	74
E285	Sodium Borate	669
E290	Carbon Dioxide	116
E296	Malic Acid	436
E297	Fumaric Acid	293
E300	Ascorbic Acid	48
E301	Sodium Ascorbate	659
E302	Calcium Ascorbate	660
E304	Ascorbyl Palmitate	51
E307	Alpha Tocopherol	32
E308	Gamma Tocopherol	34
E309	Delta Tocopherol	34
E310	Propyl Gallate	619
E311	Octyl Gallate	621
E312	Dodecyl Gallate	620
E315	Erythorbic Acid	264
E316	Sodium Erythorbate	265
E320	Butylated Hydroxyanisole	79
E321	Butylated Hydroxytoluene	81
E322	Lecithin	409
E325	Sodium Lactate	685
E330	Citric Acid Monohydrate	185
E330	Anhydrous Citric Acid	187
E331	Sodium Citrate Dihydrate	675
E332	Potassium Citrate	603
E334	Tartaric Acid	770
E338	Phosphoric Acid	530
E339	Sodium Phosphate, Dibasic	693
E339	Sodium Phosphate, Monobasic	696
E340	Dibasic Potassium Phosphate	694
E340	Monobasic Potassium Phosphate	697
E341	Calcium Phosphate, Dibasic Anhydrous	93
E341	Calcium Phosphate, Dibasic Dihydrate	96
E341	Calcium Phosphate, Tribasic	100
E385	Edetate Calcium Disodium	262
E400	Alginic Acid	21
E401	Sodium Alginate	656
E402	Potassium Alginate	594
E404	Ammonium Alginate	46
E404	Calcium Alginate	86
E405	Propylene Glycol Alginate	627
E406	Agar	14

E Number	*Excipient*	
E407	Carrageenan	124
E410	Ceratonia	148
E412	Guar Gum	315
E413	Tragacanth	785
E414	Acacia	1
E415	Xanthan Gum	821
E420	Sorbitol	718
E421	Mannitol	449
E422	Glycerin	301
E431	Polyoxyl 40 Stearate	585
E432	Polysorbate 20	580
E433	Polysorbate 80	580
E434	Polysorbate 40	580
E435	Polysorbate 60	580
E436	Polysorbate 65	580
E440	Pectin	507
E460	Cellulose, Microcrystalline	132
E460	Cellulose, Powdered	136
E461	Methylcellulose	462
E462	Ethylcellulose	278
E463	Hydroxypropyl Cellulose	336
E464	Hypromellose	346
E466	Carboxymethylcellulose Sodium	120
E471	Glyceryl Behenate	304
E491	Sorbitan Monostearate	713
E492	Sorbitan Tristearate	713
E493	Sorbitan Monolaurate	713
E494	Sorbitan Monooleate	713
E495	Sorbitan Monopalmitate	713
E500	Sodium Bicarbonate	665
E501	Potassium Bicarbonate	598
E504	Magnesium Carbonate	422
E504	Magnesium Carbonate Anhydrous	424
E504	Magnesium Carbonate Hydroxide	424
E504	Normal Magnesium Carbonate	424
E507	Hydrochloric Acid	328
E508	Potassium Chloride	600
E513	Sulfuric Acid	758
E516	Calcium Sulfate Anhydrous	105
E516	Calcium Sulfate Dihydrate	105
E516	Calcium Sulfate Hemihydrate	106
E524	Sodium Hydroxide	683
E525	Potassium Hydroxide	605

E Number	*Excipient*	
E530	Magnesium Oxide	426
E553a	Magnesium Silicate	428
E553a	Magnesium Trisilicate	434
E553a	Calcium Trisilicate Anhydrous	435
E553b	Talc	767
E558	Bentonite	58
E559	Kaolin	378
E570	Stearic Acid	737
E621	Monosodium Glutamate	480
E900	Dimethicone	244
E901	Wax, White	817
E901	Wax, Yellow	819
E903	Wax, Carnauba	809
E904	Shellac	649
E907	Wax, Microcrystalline	813
E913	Lanolin	399
E941	Nitrogen	488
E942	Nitrous Oxide	490
E943a	Butane	325
E943b	Isobutane	325
E944	Propane	325
E950	Acesulfame Potassium	4
E951	Aspartame	53
E952	Sodium Cyclamate	678
E952	Calcium Cyclamate	679
E952	Cyclamic Acid	679
E953	Isomalt	366
E954	Saccharin	638
E954	Saccharin Sodium	641
E957	Thaumatin	775
E959	Neohesperidin Dihydrochalcone	486
E965	Maltitol	438
E965	Maltitol Solution	440
E966	Lactitol	383
E967	Xylitol	824
E968	Erythritol	266
E1200	Polydextrose	542
E1201	Povidone	611
E1202	Crospovidone	214
E1440	Hydroxypropyl Starch	344
E1505	Triethyl Citrate	796
E1518	Triacetin	790
E1520	Propylene Glycol	624

Appendix III: List of Excipient ‘EINECS’ Numbers

EINECS	*Excipient*	
200-018-0	Lactic Acid	382
200-061-5	Sorbitol	720
200-066-2	Ascorbic Acid	50
200-075-1	Dextrose	233
200-075-1	Glucose, Liquid	300
200-143-0	Bronopol	77
200-210-4	Thimerosal	779
200-238-7	Chlorhexidine	166
200-289-5	Glycerin	303
200-302-4	Chlorhexidine Acetate	166
200-312-9	Palmitic Acid	502
200-313-4	Stearic Acid	739
200-317-6	Chlorobutanol	169
200-333-3	Fructose	292
200-334-9	Sucrose	747
200-338-0	Propylene Glycol	625
200-353-2	Cholesterol	183
200-431-6	Chlorocresol	173
200-449-4	Edetic Acid	262
200-456-2	Phenylethyl Alcohol	520
200-470-9	Linoleic Acid	415
200-522-0	Leucine	413
200-529-9	Edetate Calcium Disodium	262
200-532-5	Phenylmercuric Acetate	522
200-559-2	Lactose, Anhydrous	387
200-559-2	Lactose, Monohydrate	394
200-578-6	Alcohol	20
200-580-7	Acetic Acid, Glacial	7
200-618-2	Benzoic Acid	68
200-661-7	Isopropyl Alcohol	372
200-662-2	Acetone	9
200-675-3	Sodium Citrate Dihydrate	677
200-711-8	Mannitol	452
200-716-5	Maltose	448
200-772-0	Sodium Lactate	686
201-066-5	Acetyltriethyl Citrate	13
201-067-0	Acetyltributyl Citrate	11
201-069-1	Citric Acid Anhydrous	187
201-070-7	Triethyl Citrate	797
201-071-2	Tributyl Citrate	793
201-176-3	Propionic Acid	618
201-321-0	Saccharin	640
201-550-6	Diethyl Phthalate	241
201-557-4	Dibutyl Phthalate	235
201-788-0	Xylitol	827
201-793-8	Chloroxylenol	181
201-928-0	Erythorbic Acid	265
201-939-0	Menthol	461
201-944-8	Thymol	781
202-307-7	Propylparaben	631
202-318-7	Butylparaben	85
202-495-0	Monothioglycerol	483
202-598-0	Ethyl Lactate	271
202-601-5	Malic Acid	437
202-739-6	Trehalose	789
202-785-7	Methylparaben	469
202-859-9	Benzyl Alcohol	71
203-049-8	Triethanolamine	795
203-051-9	Triacetin	791
203-068-1	Phenylmercuric Borate	525
203-572-1	Propylene Carbonate	623
203-577-9	Cresol	209
203-632-7	Phenol	515
203-672-5	Dibutyl Sebacate	237
203-743-0	Fumaric Acid	294
203-743-0	Sodium Stearyl Fumarate	707
203-751-4	Isopropyl Myristate	375
203-768-7	Sorbic Acid	712
203-889-5	Ethyl Oleate	275
203-993-0	Methyl Linoleate	414
204-007-1	Oleic Acid	495
204-017-6	Stearyl Alcohol	741
204-065-8	Dimethyl Ether	247
204-214-7	Dibutyl Phthalate	235
204-399-4	Ethylparaben	289
204-402-9	Benzyl Benzoate	73
204-464-7	Ethyl Vanillin	277
204-465-2	Vanillin	799
204-479-9	Benzethonium Chloride	65
204-498-2	Propyl Gallate	621
204-589-7	Phenoxyethanol	518
204-593-9	Cetylpyridinium Chloride	158
204-648-7	2-Pyrrolidone	634
204-696-9	Carbon Dioxide	117
204-823-8	Sodium Acetate	655
204-826-4	Dimethylacetamide	254
204-881-4	Butylated Hydroxytoluene	82
205-011-6	Dimethyl Phthalate	249
205-105-7	Tartaric Acid	771
205-126-1	Sodium Ascorbate	660
205-290-4	Sodium Propionate	700
205-305-4	Ascorbyl Palmitate	52
205-316-4	Ethyl Lactate	271
205-358-3	Disodium Edetate	256
205-483-3	Monoethanolamine	479
205-500-4	Ethyl Acetate	269
205-513-5	Hexetidine	324
205-538-1	Monosodium Glutamate	481
205-571-1	Isopropyl Palmitate	377
205-582-1	Lauric Acid	407
205-597-3	Oleyl Alcohol	497
205-633-8	Sodium Bicarbonate	667
205-737-3	Erythritol	267
205-758-8	Trisodium Edetate	262
205-788-1	Sodium Lauryl Sulfate	689
206-059-0	Potassium Bicarbonate	599
206-101-8	Aluminum Stearate	42
206-376-4	Lauric Acid	407
206-988-1	Palmitic Acid	502
207-439-9	Calcium Carbonate	92
208-534-8	Sodium Benzoate	663
208-578-8	Aleuritic Acid	650
208-868-4	Ethyl Linoleate	414
208-875-2	Myristic Acid	485

EINECS	*Excipient*	
208-915-9	Magnesium Carbonate	424
209-150-3	Magnesium Stearate	432
209-151-9	Zinc Stearate	833
209-170-2	Zinc Acetate	831
209-406-4	Docusate Sodium	259
209-481-3	Potassium Benzoate	597
209-566-5	Lactitol	384
209-567-0	Maltitol	439
211-082-4	Sodium Laurate	407
211-279-5	Aluminum Stearate	43
212-487-9	Sodium Myristate	485
212-755-5	Potassium Citrate	604
212-828-1	2-Pyrrolidone	634
214-291-9	Cetrimide	154
214-620-6	Dodecyl Gallate	620
215-108-5	Bentonite	60
215-168-2	Iron Oxides	365
215-171-9	Magnesium Oxide	427
215-181-3	Potassium Hydroxide	606
215-185-5	Sodium Hydroxide	684
215-277-5	Iron Oxides	365
215-289-0	Saponite	645
215-478-8	Magnesium Aluminum Silicate	421
215-540-4	Sodium Borate Anhydrous	670
215-663-3	Sorbitan Laurate	717
215-664-9	Sorbitan Stearate	717
215-665-4	Sorbitan Oleate	717
215-681-1	Magnesium Silicate	429
215-691-6	Aluminum Oxide	38
215-710-8	Calcium Silicate	435
215-798-8	Alpha Tocopherol	34
216-472-8	Calcium Stearate	104
217-895-0	Dipotassium Edetate	261
220-491-7	Sunset Yellow FCF	198
221-450-6	Magnesium Lauryl Sulfate	689
223-026-6	Chlorhexidine Hydrochloride	166
223-095-2	Denatonium Benzoate	225
226-242-9	Octyldodecanol	493
228-973-6	Erythorbic Acid	265
230-325-5	Aluminum Stearate	43
230-636-6	Beta-carotene	197
231-211-8	Potassium Chloride	601
231-321-6	Calcium Sorbate	712
231-449-2	Sodium Phosphate, Monobasic	697
231-493-2	Cyclodextrins	220
231-545-4	Colloidal Silicon Dioxide	190
231-595-7	Hydrochloric Acid	329
231-598-3	Sodium Chloride	673
231-633-2	Phosphoric Acid	531
231-635-3	Ammonia Solution	45
231-639-5	Sulfuric Acid	759
231-673-0	Sodium Metabisulfite	691
231-783-9	Nitrogen	489
231-819-3	Sodium Sorbate	712
231-821-4	Sodium Sulfite	709
231-837-1	Calcium Phosphate, Dibasic Anhydrous	94
231-837-1	Calcium Phosphate, Dibasic Dihydrate	98
231-837-1	Calcium Phosphate, Tribasic	101
231-900-3	Calcium Sulfate	106
231-913-4	Monobasic Potassium Phosphate	697
232-273-9	Sunflower Oil	761
232-280-7	Cottonseed Oil	207
232-281-2	Corn Oil	205
232-292-2	Castor Oil, Hydrogenated	131
232-293-8	Castor Oil	129
232-302-5	Spermaceti Wax	812
232-307-2	Lecithin	411
232-313-5	Canola Oil	109

EINECS	*Excipient*	
232-315-6	Paraffin	504
232-348-6	Lanolin	400
232-360-1	Sorbitan Sesquiolate	717
232-373-2	Petrolatum	510
232-399-4	Wax, Carnauba	810
232-430-1	Lanolin Alcohols	403
232-519-5	Acacia	2
232-524-2	Carrageenan	126
232-536-8	Guar Gum	316
232-541-5	Ceratonia	149
232-549-9	Shellac	651
232-553-0	Pectin	508
232-554-6	Gelatin	297
232-658-1	Agar	15
232-674-9	Cellulose, Powdered	138
232-675-4	Dextrin	230
232-678-0	Sodium Hyaluronate	682
232-679-6	Hydroxypropyl Starch	344
232-680-1	Alginic Acid	23
232-722-9	Zein	829
232-911-6	Amylopectin	729
232-940-4	Maltodextrin	444
233-032-0	Nitrous Oxide	491
233-139-2	Boric Acid	75
234-394-2	Xanthan Gum	822
234-406-6	Quaternium 18-Hectorite	319
235-192-7	Magnesium Carbonate Hydroxide	424
235-340-0	Hectorite	319
236-550-5	Potassium Myristate	485
236-675-5	Titanium Dioxide	784
238-877-9	Talc	768
239-076-7	Magnesium Trisilicate	435
240-795-3	Potassium Metabisulfite	608
242-354-0	Chlorhexidine Gluconate	166
242-471-7	Glyceryl Tribehenate	305
243-978-6	Neohesperidin Dihydrochalcone	487
246-376-1	Potassium Sorbate	610
246-563-8	Butylated Hydroxyanisole	80
247-038-6	Glyceryl Monooleate	307
247-568-8	Sorbitan Palmitate	717
247-569-3	Sorbitan Triolate	717
247-891-4	Sorbitan Tristearate	717
249-448-0	Sorbitan Dioleate	717
250-097-0	Glyceryl Behenate	305
252-073-5	Octyl Gallate	621
253-149-0	Cetyl Alcohol	156
254-372-6	Imidurea	360
257-569-7	Sorbitan Sesquisterate	717
258-822-2	Thaumatin	776
259-141-3	Sorbitan Triisostearate	717
260-080-8	Benzalkonium Chloride	63
264-151-6	Benzalkonium Chloride	63
265-154-5	Paraffin	504
269-410-7	Sorbitan Diisostearate	717
269-919-4	Benzalkonium Chloride	63
270-325-2	Benzalkonium Chloride	63
271-536-2	Sodium Borate	670
275-126-4	Stearalkonium Hectorite	319
278-928-2	Diazolidinyl Urea	360
284-634-5	Ceratonia Extract	149
287-089-1	Benzalkonium Chloride	63
302-243-0	Attapulgite	57
303-650-6	Glyceryl Dibehenate	305
305-633-9	Stearalkonium Hectorite	319
310-127-6	Albumin	17
310-127-6	Kaolin	379
64333-34-2	*Sugartab*	749

Appendix IV: List of Excipient Molecular Weights

Mol. Weight	*Excipient*	
17.03	Ammonia Solution	44
18.02	Water	802
28.01	Nitrogen	488
36.46	Hydrochloric Acid	328
40.00	Sodium Hydroxide	683
40.30	Magnesium Oxide	426
43.82	Boric Acid (for monohydrate)	74
44.01	Carbon Dioxide	116
44.01	Nitrous Oxide	490
44.10	Propane	325
46.07	Alcohol	18
46.07	Dimethyl Ether	246
56.11	Potassium Hydroxide	605
58.08	Acetone	8
58.12	Butane	325
58.12	2-Methylpropane	325
58.44	Sodium Chloride	671
59.99	Aluminum Hydroxide Adjuvant	36
60.1	Isopropyl Alcohol	371
60.1	Propan-1-ol	372
60.05	Acetic Acid, Glacial	6
60.08	Colloidal Silicon Dioxide	188
61.08	Monoethanolamine	478
61.83	Boric Acid (for trihydrate)	74
66.05	Difluoroethane (HFC)	242
74.08	Propionic Acid	617
74.55	Potassium Chloride	600
76.09	Propylene Glycol	624
78.13	Dimethyl Sulfoxide	250
79.88	Titanium Dioxide	782
82.0	Sodium Acetate (for anhydrous)	654
84.01	Sodium Bicarbonate	665
84.31	Magnesium Carbonate	424
85.11	2-Pyrrolidone	633
86.47	Chlorodifluoromethane	175
87.12	Dimethylacetamide	253
88.1	Ethyl Acetate	268
88.85	Iron Oxides	364
90.08	Lactic Acid	381
92.09	Glycerin	301
94.11	Phenol	514
96.06	Anhydrous Sodium Propionate	700
96.06	Sodium Propionate (for anhydrous)	699
98.00	Phosphoric Acid	530
98.08	Sulfuric Acid	758
99.14	*N*-Methylpyrrolidone	634
100.09	Calcium Carbonate	89
100.11	Potassium Bicarbonate	598
100.13	Methyl Methacrylate	558
100.50	Chlorodifluoroethane (HCFC)	174
101.96	Aluminum Oxide	38
102.0	Tetrafluoroethane (HFC)	772
102.09	Propylene Carbonate	622
102.09	*(S)*-Propylene Carbonate	623
104	Methyl Lactate	271
104.07	Sodium Bisulfite	691
105.14	Diethanolamine	238
108.14	Benzyl Alcohol	69
108.14	Cresol	208
108.14	*m*-Cresol	209
108.14	*o*-Cresol	209
108.14	*p*-Cresol	209
108.16	Monothioglycerol	482
(111.1)*n* + (86.1)*m*	Copovidone	201
112.06	Sodium Lactate	685
112.13	Sorbic Acid	710
112.17	Potassium Propionate	700
114.06	Sodium Propionate (for monohydrate)	699
116.07	Fumaric Acid	293
118.13	Ethyl Lactate	270
119.98	Sodium Phosphate, Monobasic	696
120.2	Potassium Bisulfite	608
120.91	Chlorofluorocarbons (CFC)	176
122.12	Benzoic Acid	66
122.12	Erythritol	266
122.17	Phenylethyl Alcohol	519
126.04	Sodium Sulfite	708
126.11	Maltol	445
131.20	DL-Leucine	413
131.20	Leucine	412
134.09	D-Malic Acid	437
134.09	L-Malic Acid	437
134.09	Malic Acid	436
134.12	Sodium Sorbate	712
136.1	Sodium Acetate (for trihydrate)	654
136.06	Calcium Phosphate, Dibasic Anhydrous	93
136.09	Monobasic Potassium Phosphate	697
136.14	Calcium Sulfate	105
137.37	Chlorofluorocarbons (CFC)	176
137.99	Sodium Phosphate, Monobasic	696
138.16	Phenoxyethanol	517
140.14	Ethyl Maltol	272
141.96	Sodium Phosphate, Dibasic	693
142.58	Chlorocresol	171
144.11	Sodium Benzoate	662
145.14	Calcium Sulfate Hemihydrate	106
146.2	*n*-Butyl Lactate	271
149.19	Triethanolamine	794
150.09	Tartaric Acid	770
150.22	Potassium Sorbate	609
150.24	Thymol	780
152.15	Methylparaben	466
152.15	Vanillin	798
152.15	Xylitol	824
152.18	Phenoxypropanol	518
156.01	Sodium Phosphate, Monobasic	696
156.27	*d*-Menthol	460
156.27	*l*-Menthol	460
156.27	Menthol	459
156.61	Chloroxylenol	180
159.70	Iron Oxides	364

Mol. Weight	*Excipient*	
159.94	Sodium Phosphate, Dibasic	693
160.21	Potassium Benzoate	596
$(162.14)_n$	Dextrin	228
163.94	Tribasic Sodium Phosphate Anhydrous	694
166.18	Ethyl Vanillin	276
166.18	Ethylparaben	287
169.13	Monosodium Glutamate (anhydrous)	480
170.0	Heptafluoropropane (HFC)	321
170.92	Chlorofluorocarbons (CFC)	176
172.2	Capric Acid	407
172.09	Calcium Phosphate, Dibasic Dihydrate	96
172.17	Calcium Sulfate	105
172.60	Chlorophenoxyethanol	518
174.14	Methylparaben Sodium	469
174.15	Dibasic Potassium Phosphate	694
176.13	Ascorbic Acid	48
176.14	Erythorbic Acid	264
177.46	Chlorobutanol	168
177.70	Iron Oxides	364
177.98	Sodium Phosphate, Dibasic	693
179.23	Cyclamic Acid	679
180.16	Dextrose Anhydrous	233
180.16	Fructose	290
180.16	Invert Sugar	747
180.20	Propylparaben	629
180.25	Butylated Hydroxyanisole	79
182.17	Mannitol	449
182.17	Sorbitol	718
183.18	Saccharin	638
183.47	Zinc Acetate (for anhydrous)	830
186.22	Calcium Propionate	700
187.13	Monosodium Glutamate (monohydrate)	480
188.17	Ethylparaben Sodium	289
190.1	Sodium Metabisulfite	690
190.24	Glycofurol	313
190.25	Methylparaben Potassium	468
192.12	Anhydrous Citric Acid	187
193.16	Ammonium Alginate (calculated)	46
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217.24	Saccharin Sodium	641
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218.30	Propylparaben Potassium	631
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282.34	Octyl Gallate	620
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342.30	Sucrose	744
342.31	Maltose (anhydrous)	447
342.31	Trehalose (anhydrous)	788
344.5	Aluminum Monostearate	42
344.32	Isomalt (for anhydrous)	366
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358.08	Sodium Phosphate, Dibasic	693
358.20	Trisodium Edetate	262
359.16	Bentonite	58
360	Benzalkonium Chloride	61
360.31	Lactose, Monohydrate	389
360.31	Lactose, Spray-Dried (for monohydrate)	396
360.31	Maltose (monohydrate)	447
360.5	Tributyl Citrate	792
362.34	Lactitol (monohydrate)	383
364.48	Hexadecyltrimethylammonium Bromide	153
368.46	Dipotassium Edetate	261
372.2	Disodium Edetate (for dihydrate)	255
374.28	Edetate Calcium Disodium	261
376.50	Alitame (for hydrate)	28
378.33	Trehalose (dihydrate)	788
380.06	Tribasic Sodium Phosphate Dodecahydrate	694
380.20	Sodium Edetate	262
380.32	Isomalt (for dihydrate)	366
380.35	Lactitol (dihydrate)	383
381.37	Sodium Borate	669
≈383	Hectorite	318
384.45	Cetylpyridinium Bromide	158
386.67	Cholesterol	182
388.29	Imidurea (for anhydrous)	359
390.31	Calcium Ascorbate	660
390.5	Sodium Stearyl Fumarate	705
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397.64	Sucralose	742
(401.3)*n*	Sodium Hyaluronate	681
402.5	Acetyltributyl Citrate	10
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406.33	Imidurea (for monohydrate)	359
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432.57	Calcium Cyclamate	679
444.56	Docusate Sodium	257
446.59	Denatonium Benzoate (for anhydrous)	224
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591.34	Magnesium Stearate	430
594.52	Raffinose (for pentahydrate)	635
607.03	Calcium Stearate	102
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615.2	Phenylmercuric Borate	524
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